Evaluation of Retinal Nerve Fibre Layer Thickness and Choroidal Thickness in Parkinson Disease Patients

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Abstract: To evaluate the retinal nerve fibre layer (RNFL) thickness and choroidal thickness (CT) in Parkinson disease (PD) patients. A comparative cross-sectional, hospital-based study. 39 PD and 39 controls were recruited, who were gender and age matched. Subjects that fulfilled the inclusion criteria underwent optical coherence tomography for evaluation of RNFL thickness and choroidal thickness (CT). There was significant reduction of RNFL thickness in average (adjusted mean 88.87 μm vs. 94.82 μm, P=0.001), superior (adjusted mean 110.08 μm vs. 119.10 μm, P=0.002) and temporal (adjusted mean 63.77 μm vs. 70.36 μm, P=0.004) in PD compared to controls. The central subfoveal CT was significantly thinner in PD compared to controls (adjusted mean 271.13 μm vs. 285.10 μm, P=0.003). In PD group, there was significant weak negative correlation between the duration of PD with average RNFL thickness (r=–0.354, P=0.027), moderate negative correlation between the

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duration of PD with central subfoveal CT (r=–0.493, P=0.001), and weak negative correlation between the stage of PD with central subfoveal CT (r=–0.380, P=0.017). PD group had significant thinner average, superior and temporal RNFL thickness and CT compared to controls.

Introduction

Parkinson disease (PD) is a complex disease and the second most common neurodegenerative disorder after Alzheimer disease (Kalia and Lang, 2015). It was first described by James Parkinson in his "Essay on the shaking palsy" in 1817 (Parkinson, 2002). It affects one to two per 1,000 of the population and affects about 1% of people over 60 years of age (Tysnes and Storstein, 2017). PD prevalence increases with age and up to five to ten folds in those over 60 years old (Simon et al., 2020). The number of PD patients worldwide doubled from 2.5 million in 1990 to 6.1 million in 2016, and this number is estimated to double again to 12.9 million by 2040 (Dorsey, 2018; Dorsey and Bloem, 2018). The Malaysian Parkinson's Disease Association estimated about 15,000 to 20,000 PD patients in Malaysia (Bexci and Subramani, 2018).

The pathogenesis of PD is degeneration of dopaminergic neurons in substantia nigra and loss of their axons in the nigrostriatal pathway, with presence of α-synuclein containing Lewy bodies as the pathological feature (MacMahon et al., 2021). PD is primarily a motor syndrome with four cardinal signs of resting tremor, rigidity, bradykinesia, and postural instability (Jankovic, 2008). The diagnosis of PD is based on the motor symptoms and can be further categorised into Hoehn and Yahr severity staging based on the sides of involvement and severity of motor symptoms.

On the other hand, non-motor symptoms are frequently present and may even be the dominating features, including sleeping disorders, autonomic disorders, psychiatric disorders, cognitive impairment, and sensory disorders (Jankovic, 2008; Postuma et al., 2015). Visual symptoms are also part of the non-motor manifestations, including reduced contrast sensitivity, reduced colour vision, convergence insufficiency, and reading difficulty (Nowacka et al., 2014). Abd Hamid et al. (2021) observed a statistically significant reduction of visual acuity in PD patients compared to normal controls. Dopamine dysfunction in PD will affect the retina as dopaminergic amacrine cells and specific types of dopamine receptors such as D1R, D4R and D2 are found in the retina. The pathognomonic α-synuclein containing Lewy bodies are also found in the retina (Indrieri et al., 2020).

Multiple studies have been done to measure the changes in the retina in PD but have shown different results. The studies that measured the retinal nerve fibre layer (RNFL) thickness in PD patients reported contrasting findings. A meta-analysis of 32 studies on RNFL thickness in PD patients observed that most of those studies demonstrated significant thinning in certain parts of RNFL in PD group compared to normal controls, including studies by Garcia-Martin et al. (2014b), Kaur et al. (2015),

Moschos and Chatziralli (2018), Huang et al. (2021), and etc. In contrast, Tsironi et al. (2012) and Nowacka et al. (2015) did not observe any significant differences of RNFL thickness in PD group and normal controls.

Meanwhile, the choroid is the middle ocular vascular layer in between the outer sclera and inner retina. It plays an important role in the oxygenation and nutrition of the inner retina, thermal regulation of the retina, elimination of retinal waste material, and secretion of growth factors (Nickla and Wallman, 2010). Thus, the retinal functions are critically dependent on both the structural and functional health of the choroid. It has been found that the choroid is affected in many ocular diseases including Alzheimer disease, a common disorder that has been categorised together with PD under neurodegenerative disease (Bayhan et al., 2015). With the development of technology, optical coherence tomography (OCT) allows a non-invasive *in vivo* imaging of all retinal layers and choroid. Spectral-domain OCT (SD-OCT) such as Cirrus HD-OCT 5000 has been shown to be used to measure choroidal thickness (CT) (Manjunath et al., 2010).

To date, the few available studies on CT in PD have shown contrasting results. Moschos and Chatziralli (2018) and Eraslan et al. (2016) reported significant reduction of CT in PD, but Oktem et al. (2019) demonstrated the opposite finding with significant increment of CT in PD. Meanwhile, Robbins et al. (2021) did not observe any significant difference of CT in PD and normal controls.

Currently, PD is a clinical diagnosis and there is no test to make a conclusive diagnosis (Lim et al., 2012). This study is to evaluate the changes in RNFL thickness and CT in PD patients compared to normal controls. Measurement of RNFL thickness and CT might provide potential non-invasive parameters to support the diagnosis of PD and monitor the disease progression.

Material and Methods

This comparative cross-sectional study was approved by the Human Research Ethics Committee, Universiti Sains Malaysia (USM/JEPeM/20100507) and was conducted in accordance with the Declaration of Helsinki for human research.

Selection of patients

Recruitment of PD patients was conducted in the Neurology Clinic, Hospital Universiti Sains Malaysia. The sample size was calculated by PS (Power and Sample) Software version 3.1.6 by referring to studies by Satue et al. (2013) and Moschos and Chatziralli (2018). A total of 39 PD patients were recruited. Those patients were known cases of PD on treatment that met the diagnostic criteria of PD and were under Neurology Clinic follow-up. Only those who were able to communicate and undergo examinations and tests were selected. The control group consists of 39 individuals aged 50 years and older who presented to the Ophthalmology Clinic, Hospital Universiti Sains Malaysia. Only PD patients and control subjects without impaired media opacity including corneal scar, significant cataract, and

vitreous opacity that affect the quality of OCT images were included in this study. Subjects who had pre-existing optic neuropathy, retinopathy, maculopathy, history of trauma or previous ocular surgery, and systemic disease such as cerebral vascular accident, intracranial lesion, neurological and demyelinating diseases were excluded. All participants who consented to take part in the study underwent visual acuity assessment, thorough ocular examinations, and fundus evaluation with slit lamp biomicroscope (Topcon Corp, Japan). Intraocular pressure measurement was performed to rule out ocular pathology such as glaucoma or ocular hypertension, which would have precluded participation in the study. All participants were then subjected to OCT (Zeiss Cirrus HD-OCT 5000) examination for RNFL thickness and CT for the right eye.

Optical coherence tomography (OCT)

OCT examinations for RNFL thickness and CT of the right eye were performed using the Zeiss Cirrus HD-OCT 5000 machine. Both tests were performed by a single well-trained operator (optometrist). Only the test or repeated test that yielded a signal strength of ≥ 6/10 was taken for interpretations to ensure the accuracy of the results. Measurements of the average, superior, inferior, nasal, and temporal RNFL thickness will be automatically generated by the machine. As for the measurement of CT, the setting of the OCT would be changed to HD 1-line 100× beforehand, then the foveal centre would be focused, and a single high-definition raster scan would be generated. The central subfoveal CT was then carefully measured manually using the Cirrus linear measurement tool from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium to the inner surface of the sclera.

Statistical analysis

Data analysis was performed using the IBM SPSS statistics version 27.0 (IBM Corp., Armonk, Chicago, IL, USA). Descriptive analysis was used for the mean values and standard deviation (SD). For demographic data, they will be tested for comparison of age, race and gender. The Student's *t*-test and Pearson's chi-square test were used to analyse the demographic data. Independent *t*-test was used to compare

Table 1 – Evans strength of correlation

Coefficient value (r)	Strength of correlation
0.00–0.19	very weak
0.20–0.39	weak
0.40–0.59	moderate
0.60–0.79	strong
0.80–1.00	very strong

the means of RNFL thickness and central subfoveal CT. All P-values of < 0.05 were considered statistically significant. Analysis of covariance (ANCOVA) was used to control potential confounding factors, namely age, gender and underlying medical illness. Pearson correlation analysis was used to determine the correlation coefficient (r) of the association of the duration and stage of PD with the average RNFL thickness and CT. General guidelines for assigning strength of correlation by Evans (1996) will be used (Table 1). A value > 0 indicates a positive association whereas a value < 0 indicates a negative association. P-value < 0.05 was considered as statistically significant.

Results

The distribution of demographic data is shown in Table 2. There was a total of 78 participants, which were comprised of 39 PD patients and 39 controls. Among them, 51 were male, while 27 were female. PD group comprised of 27 males and 12 females, while the control group had 24 males and 15 females. The age of the participants ranged from 50 to 73 years old, with a mean age of 62.5 ± 5.2 years for PD patients and 63.4 ± 6.5 years for controls. PD and control groups were gender and age matched as the discrepancy was not statistically significant (P=0.475 for gender, P=0.519 for age). 74 of the participants were Malay and 4 were Chinese. Among the 39 PD patients, the mean duration of PD was 4.7 years ± 1.6 while the mean stage of PD was 2.9 ± 0.6.

Table 2 – Demographic data of PD patients and controls

	PD (n=39)	Controls (n=39)	P-value*
Mean age (year) – mean (SD)	62.5 (5.2)	63.4 (6.5)	0.519[a]
Gender – n (%)			0.475[b]
Male	27 (69.2)	24 (61.5)	
Female	12 (30.8)	15 (38.5)	
Race – n (%)			0.040[b]
Malay	39 (100.0)	35 (89.7%)	
Chinese	0 (0.0)	4 (10.3%)	
Medical illness – n (%)			0.346[b]
No medical illness	10 (25.6)	13 (33.3)	
Diabetes mellitus	8 (20.5)	9 (23.1)	
Hypertension	14 (35.9)	7 (17.9)	
Multiple medical illness	7 (17.9)	10 (25.6)	
Mean duration of PD (year) – mean (SD)	4.7 (1.6)	–	–
Mean stage of PD – mean (SD)	2.9 (0.6)	–	–

[a]independent *t*-test; [b]Pearson's chi-square test; *P<0.05 significant; PD – Parkinson disease; SD – standard deviation

Table 3 – Comparison of mean RNFL thickness of right eye between PD patients and controls

RNFL	PD (n=39)		Control (n=39)		Adj. mean differences (95% CI)	df	P-value*
	mean (SD)[a]	adj. mean[b] (95% CI)	mean (SD)[a]	adj. mean[b] (95% CI)			
Average (μm)	89.36 (9.00)	88.87 (86.36, 91.38)	94.33 (11.00)	94.82 (92.32, 97.33)	–5.95 (–9.51, –2.40)	73.1	**0.001**
Superior (μm)	110.56 (12.88)	110.08 (106.07, 114.09)	118.62 (13.82)	119.10 (115.09, 123.11)	–9.03 (–14.72, –3.34)	75.6	**0.002**
Inferior (μm)	116.77 (10.52)	115.81 (111.38, 120.25)	120.44 (25.83)	121.39 (116.96, 125.83)	–5.58 (–11.87, 0.72)	50.2	0.081
Temporal (μm)	64.41 (11.84)	63.77 (60.64, 66.90)	69.72 (11.73)	70.36 (67.23, 73.49)	–6.59 (–11.03, –2.15)	76.0	**0.004**
Nasal (μm)	65.95 (14.41)	66.05 (62.42, 69.68)	68.72 (10.51)	68.62 (64.99, 72.25)	–2.57 (–7.72, 2.58)	69.5	0.323

[a]independent *t*-test; [b]adjusted mean using ANCOVA after controlling for age, gender and underlying medical illness; *P<0.05 significant; RNFL – retinal nerve fibre layer; PD – Parkinson disease; CI – confidence interval; SD – standard deviation; adj. – adjusted

The mean RNFL thickness of PD patients and controls is reflected in Table 3. We observed a lower mean RNFL thickness in the average and all four quadrants in the PD group when compared to the control group. After controlling for potential confounders which are age, gender, and underlying medical illness using ANCOVA, there was a decrease in the mean RNFL thickness in the average and all four quadrants. However, a statistically significant reduction was only noticed in the average (adjusted mean 88.87 μm; 95% CI [confidence interval] = 86.36, 91.38 vs. 94.82 μm; 95% CI = 92.32, 97.33; P=0.001), superior (adjusted mean 110.08 μm; 95% CI = 106.07, 114.09 vs. 119.10 μm; 95% CI = 115.09, 123.11; P=0.002) and temporal (adjusted mean 63.77 μm; 95% CI = 60.64, 66.90 vs. 70.36 μm; 95% CI = 67.23, 73.49; P=0.004) quadrants but not in the inferior and nasal quadrants in the PD group as compared to the controls.

The comparison of the mean central subfoveal CT between PD patients and controls is shown in Table 4. The central subfoveal CT was thinner in PD group as compared to the controls. After controlling potential confounders which are age, gender and underlying medical illness using ANCOVA, there was a significant reduction in the central subfoveal CT in PD group as compared to the controls (adjusted mean 271.13 μm; 95% CI = 264.67, 277.60 vs. 285.10 μm; 95% CI = 278.63, 291.56; P=0.003).

Table 5 shows the correlation between the duration of PD with average RNFL thickness in PD patients. There was a statistically significant weak negative correlation between them (r=–0.354, P=0.027).

Table 4 – Comparison of mean central subfoveal CT of right eye between PD patients and controls

CT	PD (n=39)		Control (n=39)		Adj. mean differences (95% CI)	df	P-value*
	mean (SD)[a]	adj. mean[b] (95% CI)	mean (SD)[a]	adj. mean[b] (95% CI)			
Central subfoveal CT (μm)	272.13 (14.82)	271.13 (264.67, 277.60)	284.13 (27.99)	285.10 (278.63, 291.56)	–13.96 (–23.13, –4.79)	57.8	**0.003**

[a]independent *t*-test; [b]adjusted mean using ANCOVA after controlling for age, gender and underlying medical illness; *P<0.05 significant; CT – choroidal thickness; PD – Parkinson disease; CI – confidence interval; SD – standard deviation; adj. – adjusted

Table 5 – Correlation between duration of PD with average RNFL thickness in PD patients

Parameter	Pearson's correlation (r)	P-value*
Average RNFL thickness (μm)	–0.354	**0.027**

*P<0.05 significant; RNFL – retinal nerve fibre layer; PD – Parkinson disease

Table 6 – Correlation between stage of PD with average RNFL thickness in PD patients

Parameter	Pearson's correlation (r)	P-value*
Average RNFL thickness (μm)	–0.253	0.120

*P<0.05 significant; RNFL – retinal nerve fibre layer; PD – Parkinson disease

Table 7 – Correlation between duration of PD with central subfoveal CT in PD patients

Parameter	Pearson's correlation (r)	P-value*
Central subfoveal CT (μm)	–0.493	**0.001**

*P<0.05 significant; PD – Parkinson disease; CT – choroidal thickness

Table 8 – Correlation between stage of PD with central subfoveal CT in PD patients

Parameter	Pearson's correlation (r)	P-value*
Central subfoveal CT (μm)	–0.380	**0.017**

*P<0.05 significant; PD – Parkinson disease; CT – choroidal thickness

Table 6 shows the correlation between the stage of PD with average RNFL thickness in PD patients. There was a weak negative correlation, however it was not statistically significant (r=–0.253, P=0.120).

Table 7 shows the correlation between the duration of PD with central subfoveal CT in PD patients. There was a statistically significant moderate negative correlation between them (r=–0.493, P=0.001).

Table 8 shows the correlation between the stage of PD with central subfoveal CT in PD patients. There was a statistically significant weak negative correlation between them (r=–0.380, P=0.017).

Discussion

PD is characterised by motor symptoms of tremor, rigidity, bradykinesia, and postural instability, however, visual disturbance such as impairment of visual acuity, reduction of contrast sensitivity and reading difficulty are also frequently reported among PD patients (Bodis-Wollner, 2013; Weil et al., 2016). Studies have shown that the prevalence of having at least one visual symptom among PD patients was 77.3% to 82% (Urwyler et al., 2014; Borm et al., 2020). The pathogenesis of PD is the loss of dopaminergic neurons in the substantia nigra and depletion of their axons in the nigrostriatal pathway, with the presence of Lewy bodies as the pathognomonic histopathological sign (MacMahon et al., 2021). Dopaminergic cells and dopamine receptors are also found in the retina (Indrieri et al., 2020). α-synuclein is a protein that forms a main part of Lewy bodies, and it is harmful to the retina (Indrieri et al., 2020; MacMahon et al., 2021). An autopsy study has found that this protein accumulated in the retina of all nine PD patients and none of the six controls (Ortuño-Lizarán et al., 2018). On the other hand, the choroid which forms the ocular vascular layer has been found to be abnormal in many ocular diseases, including another common neurodegenerative disorder, the Alzheimer disease (Bayhan et al., 2015). However, to date, the few available studies on the CT in PD patients are contradictory (Eraslan et al., 2016; Moschos and Chatziralli, 2018; Satue et al., 2018; Brown et al., 2021; Robbins et al., 2021).

The demographic profile of our study showed the mean age of our PD patients as 62.5 ± 5.2 years and 63.4 ± 6.5 years for controls. Both groups were age-matched as there was no significant difference between their mean ages. Most of the participants in this study were Malays, as our study was done in Kelantan. According to the Department of Statistics Malaysia, 96.0% of the estimated population of Kelantan in 2021 was Malays (Department of Statistics Malaysia, 2021). No significant discrepancies in gender and underlying medical illness between PD patients and controls. Within the PD group, the number of men was over two times that of women (male = 27, female = 12), which was higher than the PD prevalence with a male to female ratio of 1.48 reported in a meta-analysis (Moisan et al., 2016). This disparity occurred by chance, there was no bias in selection. Age, gender and underlying medical illness had been included in the analysis by ANCOVA as potential confounding factors.

In terms of RNFL thickness, our result showed reduction in all four quadrants in PD patients as compared to controls. The reduction was statistically significant in the average RNFL thickness with a mean difference of –5.95 μm (P=0.001), superior RNFL quadrant with a mean difference of –9.03 μm (P=0.002) and temporal RFNL quadrant with a mean difference of –6.59 (P=0.004) after controlling the potential confounding factors. Our result is comparable to a meta-analysis of 32 studies on RNFL in PD patients, where most of those studies reported thinning in the average and some RNFL quadrants, and only three studies showed reduction of the average and all four RNFL quadrants. After pooling and re-analysing the data, the pooled mean difference revealed reduction in the average and all four RNFL quadrants in PD patients compared to controls, with the amplitude of reduction in the inferior more than the superior, and more in the temporal than the nasal quadrant. By comparing to a meta-analysis of 24 studies on Alzheimer disease which reported RNFL thinning in an opposing order (greater reduction in superior than inferior and nasal than temporal), they postulated the possibility of using this pattern of RNFL thinning to differentiate PD from other neurodegenerative disorders (Chan et al., 2019; Huang et al., 2021).

Another meta-analysis published in 2014 that included some earlier studies (13 studies in total, five overlapped with the studies in the formerly mentioned meta-analysis) also showed similar results with an identical pattern of RNFL thinning after analysing the pooled data, namely the reduction was more in the inferior than the superior, and more in the temporal than the nasal quadrant. They attributed this greater reduction in the temporal quadrant to involvement of the papillomacular bundle, which is typically susceptible to neurodegenerative diseases (Yu et al., 2019). To date, most of the available studies demonstrated RNFL thinning in PD patients. Garcia-Martin et al. (2014b) reported significant thinning in the average, superior, inferior, and temporal quadrants. Studies by Moschos and Chatziralli (2018) and Kaur et al. (2015) both found significant thinning in average, superior and temporal quadrants. A more recent study by Abd Hamid et al. (2021) showed significant thinning in average, superior and inferior quadrants. Satue et al. (2013) found significant thinning only in the inferior quadrant. The study by Pilat et al. (2016) is one of the few that reported significant thinning in average and all four quadrants. These studies postulated that progressive retinal dopaminergic cell loss causes atrophy of their axons, and subsequently leading to corresponding RNFL thinning. Garcia-Martin et al. (2014a) demonstrated a more prominent mean RNFL thinning correlated with a thinner mean ganglion cell layer. On the other hand, Tsironi et al. (2012) found no significant difference between PD patients and controls. They attributed this dissimilarity to differences in study population, sample size, disease stage and imaging device (Tsironi et al., 2012). Nowacka et al. (2015) also reported similar results.

Our results showed a significant weak negative correlation between the duration of PD with average RNFL thickness in PD patients (r=–0.354, P=0.027). There was

also a weak negative correlation between the Hoehn and Yahr severity stage of PD with the average RNFL thickness but not statistically significant (r=–0.253, P=0.120). Our results are comparable to study by Sengupta et al. (2018) that found a significant correlation between disease duration and RNFL thickness and attributed this finding to the simultaneous neurodegeneration in both the brain and retina. However, like our results, they also did not observe any significant correlation between severity and RNFL thickness. They related this discrepancy to their small sample size of 34 PD patients (Sengupta et al., 2018). Similarly, Atum and Demiryürek (2021) also did not find any significant correlation between Hoehn and Yahr severity staging average RNFL. Contrary to our result, Garcia-Martin et al. (2014b) reported a significant negative correlation between the severity stage of PD with certain parts of RNFL thickness but not with the duration of disease. Meanwhile, Cubo et al. (2014) did not find any significant association between severity stage and RNFL thickness in PD patients. Anyway, several studies have demonstrated significant reduction of RNFL thickness when they followed up PD patients over two, three and five years respectively to signify the progressive anatomical changes together with disease progression (Satue et al., 2017; Atum and Demiryürek, 2021; Kamata et al., 2022).

In terms of central subfoveal CT, our results showed statistically significant reduction in PD patients compared to controls, with a mean difference of –13.96 μm (P=0.003) after controlling the potential confounding factors. Our result is consistent with the study by Moschos and Chatziralli (2018) that attributed their finding to the synergistic outcome of vascular abnormalities and neurodegeneration that might be potentially responsible for clinical risk and disease progression. Eraslan et al. (2016) also revealed similar result and attributed it to the disease-related hypoperfusion due to choroidal blood flow abnormalities, the hypotensive effect of dopamine agonist and reduction of metabolic activity secondary to retinal ganglion cell loss. Kamata et al. (2022) observed a comparable result and related it to autonomic dysfunction in PD leading to the reduction of choroidal blood flow. In contrast to our study, Oktem et al. (2019) demonstrated a significant thickening of central subfoveal CT in PD patients compared to controls and related it to the increment of perivascular connective tissue and enlargement of perivascular spaces in PD patients. Satue et al. (2018) also observed thicker central subfoveal choroid in PD patients, but not statistically significant. Meanwhile, Robbins et al. (2021) did not find any significant changes in the central subfoveal CT between PD patients and controls. However, they observed significant differences between the two groups in terms of other choroidal parameters, including total choroidal area, luminal area, and choroidal vascularity index. They postulated choroidal vascularity abnormalities occurred without changes in CT (Robbins et al., 2021).

The correlation analysis between the duration of PD and central subfoveal CT in PD patients revealed a statistically significant moderate negative correlation between them (r=–0.493, P=0.001). Similarly, there was also a statistically significant weak negative correlation between the Hoehn and Yahr severity stage of PD and central

subfoveal CT in PD patients (r=–0.380, P=0.017). Eraslan et al. (2016) observed a significant negative correlation between duration of PD with CT. However, there was no correlation between the severity and CT (Eraslan et al., 2016). Contrary to our study, Oktem et al. (2019) found no correlation between the duration of PD and CT.

Limitations and recommendations

While conducting our study, we identified several limitations. First, this was a cross-sectional study and there was no follow-up to compare the changes in all the studied parameters over time. We suggest a longitudinal study with repeated OCT on the same patients to be done in the future to evaluate the possible progress in RNFL thickness and CT in the long term, probably over a minimum of two years, as Atum and Demiryürek (2021) who followed up subjects every six months only started to observe a significant reduction in RNFL thickness at two years duration.

Second, our patient selection was limited by the motor dysfunction in some PD patients. Hoehn and Yahr staging classifies PD into five severity stages. However, we were only able to include those in stage two to four. The characteristic motor symptoms in PD had hindered us from capturing a proper OCT image in some PD patients, especially those in stage five, as they could not maintain the steady positioning and focusing that were very much required while performing the OCT. We suggest including patients with severe stages to be included in future studies, probably with more advanced and patient-friendly devices to better study the changes in RNFL thickness and CT.

Third, we conducted our study in only one centre in Kelantan, with Malays contributing to 96.0% of the local population. This might cause population bias and affect the accuracy of the results. We suggest a multi-centred study with a larger sample size and include various ethics to better study the effect of PD on the studied parameters.

Conclusion

Our study showed that PD patients have a statistically significant reduction of RNFL thickness in the average, superior, and temporal quadrants when compared to controls. There was also a significant reduction in central subfoveal CT in PD patients compared to controls. Thus, we believe RNFL thickness and CT might be useful non-invasive parameters to help to support the diagnosis of PD and monitor the disease progression.

References

Abd Hamid, M. R., Wan Hitam, W. H., Abd Halim, S. (2021) Retinal nerve fiber layer and macular thickness in Parkinson's disease patients. *Cureus* **13(7)**, e16224.

Atum, M., Demiryürek, B. E. (2021) Retinal morphological changes during the two years of follow-up in Parkinson's disease. *Ideggyogy. Sz*. **74(1–2)**, 57–63.

Bayhan, H. A., Aslan Bayhan, S., Celikbilek, A., Tanık, N., Gürdal, C. (2015) Evaluation of the chorioretinal thickness changes in Alzheimer's disease using spectral-domain optical coherence tomography. *Clin. Exp. Ophthalmol*. **43(2)**, 145–151.

Bexci, M. S., Subramani, R. (2018) Decoding Parkinson's associated health messages in social media pages by Malaysian service administrators. *Malaysian Journal of Medical Research* **2(4)**, 64–72.

Bodis-Wollner, I. (2013) Foveal vision is impaired in Parkinson's disease. *Parkinsonism Relat. Disord*. **19**, 1–14.

Borm, C. D. J. M., Visser, F., Werkmann, M., de Graaf, D., Putz, D., Seppi, K., Collerton, D., Thomas, A., Burn, D., McKeith, I., Mosimann, U. P. (2020) Seeing ophthalmologic problems in Parkinson disease. Results of a visual impairment questionnaire. *Neurology* **94(14)**, e1539–e1547.

Brown, G. L., Camacci, M. L., Kim, S. D., Grillo, S., Nguyen, J. V., Brown, D. A., Ullah, S. P., Lewis, M. M., Du, G., Kong, L., Sundstrom, J. M., Huang, X., Bowie, E. M. (2021) Choroidal thickness correlates with clinical and imaging metrics of Parkinson's disease: A pilot study. *J. Parkinsons Dis*. **11(4)**, 1857–1868.

Chan, V. T. T., Sun, Z., Tang, S., Chen, L. J., Wong, A., Tham, C. C., Wong, T. Y., Chen, C., Ikram, M. K., Whitson, H. E., Lad, E. M., Mok, V. C. T., Cheung, C. Y. (2019) Spectral-domain OCT measurements in Alzheimer's disease: A systematic review and meta-analysis. *Ophthalmology* **126(4)**, 497–510.

Cubo, E., López Peña, M. J., Diez-Feijo, V. E., Pérez, G. O., Garcia, G. P., Araus, G. E., Prieto, T. R., Mariscal, P. N., Armesto, D. (2014) Lack of association of morphologic and functional retinal changes with motor and non-motor symptoms severity in Parkinson's disease. *J. Neural Transm. (Vienna)* **121(2)**, 139–145.

Department of Statistics Malaysia (2021) Current population estimates, Malaysia, 2021.

Dorsey, E. R. (2018) Global, regional, and national burden of Parkinson's disease, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. **17(11)**, 939–953.

Dorsey, E. R., Bloem, B. R. (2018) The Parkinson pandemic – A call to action. *JAMA Neurol*. **75(1)**, 9–10.

Eraslan, M., Cerman, E., Yildiz Balci, S., Celiker, H., Sahin, O., Temel, A., Suer, D., Tuncer Elmaci, N. (2016) The choroid and lamina cribrosa is affected in patients with Parkinson's disease: Enhanced depth imaging optical coherence tomography study. *Acta Ophthalmol*. **94(1)**, e68–e75.

Evans, J. D. (1996) *Straightforward Statistics for the Behavioral Sciences*. Brooks/Cole Publishing, Pacific Grove.

Garcia-Martin, E., Larrosa, J. M., Polo, V., Satue, M., Marques, M. L., Alarcia, R., Seral, M., Fuertes, I., Otin, S., Pablo, L. E. (2014a) Distribution of retinal layer atrophy in patients with Parkinson disease and association with disease severity and duration. *Am. J. Ophthalmol*. **157(2)**, 470–478.e2.

Garcia-Martin, E., Rodriguez-Mena, D., Satue, M., Almarcegui, C., Dolz, I., Alarcia, R., Seral, M., Polo, V., Larrosa, J. M., Pablo, L. E. (2014b) Electrophysiology and optical coherence tomography to evaluate Parkinson disease severity. *Invest. Ophthalmol. Vis. Sci*. **55(2)**, 696–705.

Huang, L., Wang, C., Wang, W., Wang, Y., Zhang, R. (2021) The specific pattern of retinal nerve fiber layer thinning in Parkinson's disease: A systematic review and meta-analysis. *J. Neurol*. **268(11)**, 4023–4032.

Indrieri, A., Pizzarelli, R., Franco, B., De Leonibus, E. (2020) Dopamine, alpha-synuclein, and mitochondrial dysfunctions in Parkinsonian eyes. *Front. Neurosci*. **14**, 567129.

Jankovic, J. (2008) Parkinson's disease: Clinical features and diagnosis. *J. Neurol. Neurosurg. Psychiatry* **79(4)**, 368–376.

Kalia, L. V., Lang, A. E. (2015) Parkinson's disease. *Lancet* **386**, 896–912.

Kamata, Y., Hara, N., Satou, T., Niida, T., Mukuno, K. (2022) Investigation of the pathophysiology of the retina and choroid in Parkinson's disease by optical coherence tomography. *Int. Ophthalmol*. **42(5)**, 1437–1445.

Kaur, M., Saxena, R., Singh, D., Behari, M., Sharma, P., Menon, V. (2015) Correlation between structural and functional retinal changes in Parkinson disease. *J. Neuroophthalmol*. **35(3)**, 254–258.

Lim, S. Y., Norlinah, M. I., Santhi, D. P., Lee, M. K., Chee, K. Y., Shanthi, V., Tan, A. H., Chris, C. K. T., Kamal, A. A. (2012) *2012 Consensus Guidelines for the Treatment of Parkinson's Disease*. Available at: https://www.neuro.org.my/assets/guideline/2013PD_08012013.pdf

MacMahon, C. A. N., McComish, S. F., Fletcher, J. M., Caldwell, M. A. (2021) The pathogenesis of Parkinson's disease: A complex interplay between astrocytes, microglia, and T lymphocytes? *Front. Neurol*. **12**, 1–20.

Manjunath, V., Taha, M., Fujimoto, J. G., Duker, J. S. (2010) Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography. *Am. J. Ophthalmol*. **150(3)**, 325–329.e1.

Moisan, F., Kab, S., Mohamed, F., Canonico, M., Le Guern, M., Quintin, C., Carcaillon, L., Nicolau, J., Duport, N., Singh-Manoux, A., Boussac-Zarebska, M., Elbaz, A. (2016) Parkinson disease male-to-female ratios increase with age: French nationwide study and meta-analysis. *J. Neurol. Neurosurg. Psychiatry* **87(9)**, 952–957.

Moschos, M. M., Chatziralli, I. P. (2018) Evaluation of choroidal and retinal thickness changes in Parkinson's disease using spectral domain optical coherence tomography. *Semin. Ophthalmol*. **33(4)**, 494–497.

Nickla, D. L., Wallman, J. (2010) The multifunctional choroid. *Prog. Retin. Eye Res*. **29(2)**, 144–168.

Nowacka, B., Lubinski, W., Honczarenko, K., Potemkowski, A., Safranow, K. (2014) Ophthalmological features of Parkinson disease. *Med. Sci. Monit*. **20**, 2243–2249.

Nowacka, B., Lubiński, W., Honczarenko, K., Potemkowski, A., Safranow, K. (2015) Bioelectrical function and structural assessment of the retina in patients with early stages of Parkinson's disease (PD). *Doc. Ophthalmol*. **131(2)**, 95–104.

Oktem, C., Oktem, E., Kurt, A., Kilic, R. (2019) Does choroidal thickness change in Parkinson's disease? *Cesk. Slov. Neurol. N* **82(6)**, 677–681.

Ortuño-Lizarán, I., Beach, T. G., Serrano, G. E., Walker, D. G., Adler, C. H., Cuenca, N. (2018) Phosphorylated α-synuclein in the retina is a biomarker of Parkinson's disease pathology severity. *Mov. Disord*. **33(8)**, 1315–1324.

Parkinson, J. (2002) An essay on the shaking palsy. *J. Neuropsychiatry Clin. Neurosci*. **14(2)**, 223–236.

Pilat, A., McLean, R. J., Proudlock, F. A., Maconachie, G. D., Sheth, V., Rajabally, Y. A., Gottlob, I. (2016) *In vivo* morphology of the optic nerve and retina in patients with Parkinson's disease. *Invest. Ophthalmol. Vis. Sci*. **57(10)**, 4420–4427.

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., Deuschl, G. (2015) MDS clinical diagnostic criteria for Parkinson's disease. *Mov. Disord*. **30(12)**, 1591–1601.

Robbins, C. B., Thompson, A. C., Bhullar, P. K., Koo, H. Y., Agrawal, R., Soundararajan, S., Yoon, S. P., Polascik, B. W., Scott, B. L., Grewal, D. S., Fekrat, S. (2021) Characterization of retinal microvascular and choroidal structural changes in Parkinson disease. *JAMA Ophthalmol*. **139(2)**, 182–188.

Satue, M., Garcia-Martin, E., Fuertes, I., Otin, S., Alarcia, R., Herrero, R., Bambo, M. P., Pablo, L. E., Fernandez, F. J. (2013) Use of Fourier-domain OCT to detect retinal nerve fiber layer degeneration in Parkinson's disease patients. *Eye (Lond.)* **27(4)**, 507–514.

Satue, M., Rodrigo, M. J., Obis, J., Vilades, E., Gracia, H., Otin, S., Fuertes, M. I., Alarcia, R. C., Crespo, J. A., Polo, V., Larrosa, J. M., Pablo, L. E., Garcia-Martin, E. (2017) Evaluation of progressive visual dysfunction and retinal degeneration in patients with Parkinson's disease. *Invest. Ophthalmol. Vis. Sci*. **58(2)**, 1151–1157.

Satue, M., Obis, J., Alarcia, R., Orduna, E., Rodrigo, M. J., Vilades, E., Gracia, H., Otin, S., Fuertes, M. I., Polo, V., Larrosa, J. M., Pablo, L. E., Garcia-Martin, E. (2018) Retinal and choroidal changes in patients with Parkinson's disease detected by Swept-source optical coherence tomography. *Curr. Eye Res*. **43(1)**, 109–115.

Sengupta, P., Dutta, K., Ghosh, S., Mukherjee, A., Pal, S., Basu, D. (2018) Optical coherence tomography findings in patients of Parkinson's disease: An Indian perspective. *Ann. Indian Acad. Neurol*. **21(2)**, 150–155.

Simon, D. K., Tanner, C. M., Brundin, P. (2020) Parkinson disease epidemiology, pathology, genetics, and pathophysiology. *Clin. Geriatr. Med*. **36(1)**, 1–12.

Tsironi, E. E., Dastiridou, A., Katsanos, A., Dardiotis, E., Veliki, S., Patramani, G., Zacharaki, F., Ralli, S., Hadjigeorgiou, G. M. (2012) Perimetric and retinal nerve fiber layer findings in patients with Parkinson's disease. *BMC Ophthalmol*. **12**, 54.

Tysnes, O.-B., Storstein, A. (2017) Epidemiology of Parkinson's disease. *J. Neural Transm. (Vienna)* **124(8)**, 901–905.

Urwyler, P., Nef, T., Killen, A., Collerton, D., Thomas, A., Burn, D., McKeith, I., Mosimann, U. P. (2014) Visual complaints and visual hallucinations in Parkinson's disease. *Parkinsonism Relat. Disord*. **20(3)**, 318–322.

Weil, R. S., Schrag, A. E., Warren, J. D., Crutch, S. J., Lees, A. J., Morris, H. R. (2016) Visual dysfunction in Parkinson's disease. *Brain* **139(11)**, 2827–2843.

Yu, J.-G., Feng, Y.-F., Xiang, Y., Huang, J.-H., Savini, G., Parisi, V., Yang, W.-J., Fu, X.-A. (2019) Retinal nerve fiber layer thickness changes in Parkinson disease: A meta-analysis. *PLoS One* **9(1)**, e85718.