EVALUATION OF RETINAL NERVE FIBRE LAYER THICKNESS AND CHOROIDAL THICKNESS IN PARKINSON DISEASE PATIENTS

By

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledge. I declare that I have no financial of interest in the instruments and the computer software in this study.

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ABSTRAK

Pengenalan

Parkinson Disease (PD) atau penyakit Parkinson merupakan penyakit neurodegenerasi yang dicirikan oleh gejala pergerakan tertentu. Gejala penglihatan juga sering terlibat. Retina manusia dianggapkan sebagai sebahagian daripada system saraf pusat. Koroid merupakan lapisan pembuluh darah mata yang memainkan peranan penting dalam fungsi retina. Perubahan di lapisan retina dan koroid mungkin berlaku di kalangan pesakit Parkinson. Ketebalan lapisan gentian saraf retina (LGSR) dan ketebalan lapisan koroid (LK) bermungkinan dijadikan parameter tambahan untuk diagnosis penyakit Parkinson. Kajian ini memperkenalkan potensi ketebalan LGSR dan ketebalan LK sebagai biomarker neurodegenerasi untuk pesakit Parkinson.

Objektif

Objectif kajian ini adalah untuk mengkaji ketebalan LGSR dan ketebalan LK di kalangan pesakit Parkinson.

Kaedah kajian

Sebuah kajian perbandingan keratan rentas telah dijalankan di Hospital Universiti Sains Malaysia yang melibatkan seramai 39 orang pesakit Parkinson dan 39 orang subjek kawalan yang dipadankan dari segi jantina dan umur. Peserta yang memenuhi syarat kemasukan menjalani pemeriksaan mata dan pemeriksaan *optical coherence tomography* (OCT) pada mata kanan untuk mengukur ketebalan LGSR dan ketebalan LK. Untuk

analisa statistic, kaedah *Independent t-test*, *chi-square*, ANCOVA dan *Pearson's correlation* digunakan.

Keputusan

Terdapat penipisan yang signifikan pada LGSR di kalangan pesakit Parkinson berbanding dengan subjek kawalan di ketebalan purata (min ubah 88.87µm; 95% CI = 86.36, 91.38 berbanding 94.82µm; 95% CI = 92.32, 97.33; *P* = 0.001), kuadran atas (min ubah 110.08µm; 95% CI = 106.07, 114.09 berbanding 119.10µm; 95% CI = 115.09, 123.11; *P* = 0.002) dan temporal (min ubah 63.77µm; 95% CI = 60.64, 66.90 berbanding 70.36µm; 95% CI = 67.23, 73.49; *P* = 0.004). Terdapat penipisan yang signifikan di LK di bawah fovea pusat (min ubah 271.13µm; 95% CI = 264.67, 277.60 berbanding 285.10µm; 95% CI = 278.63, 291.56; *P* = 0.003) di kalangan pesakit Parkinson berbanding dengan subjek kawalan. Terdapat korelasi negatif yang lewah dan signifikan antara tempoh menghidapi penyakit PD dengan ketebalan LGSR purata (*r* = -0.354, *P* = 0.027). Terdapat korelasi negatif yang sederhana dan signifikan antara tempoh menghidapi penyakit PD dengan ketebalan LK di bawah fovea pusat (*r* = -0.493, *P* = 0.001), dan kolerasi negatif yang lewah dan signifikan antara peringkat penyakit PD dengan ketebalan LK di bawah fovea pusat (*r* = -0.380, *P* = 0.017).

Kesimpulan

Pesakit Parkinson mempunyai purata ketebalan LGSR yang lebih nipis di purata, kuadran atas dan kuadran temporal dan juga ketebalan LK berbanding dengan subjek kawalan.

Katakunci

Penyakit Parkinson, ketebalan lapisan gentian saraf retina, ketebalan lapisan koroid, kolerasi, *optical coherence tomography*, penyakit neurodegenerasi

ABSTRACT

Introduction

Parkinson Disease (PD) is a neurodegenerative disorder characterised by specific motor features. Visual symptoms are also frequently involved. The human retina is considered part of the central nervous system in humans. Choroid is the ocular vascular layer that plays an important role in retina function. Anatomical changes in the retina and choroid may occur in patients diagnosed with neurodegenerative disorders such as PD. Retinal nerve fibre layer (RNFL) thickness and choroidal thickness (CT) could be additional useful parameters to diagnose PD. By conducting this study, we hope to highlight the potential of RNFL thickness and CT analysis as neurodegenerative biomarkers for PD.

Objective

To evaluate the RNFL thickness and CT in PD patients.

Methodology

A comparative cross-sectional, hospital-based study was conducted at Hospital Universiti Sains Malaysia. There were 39 PD patients and 39 normal controls recruited. These 2 groups were gender and age matched. Subjects that fulfilled the inclusion criteria underwent ocular examinations and optical coherence tomography (OCT) examinations in the right eye for peripapillary RNFL thickness and CT evaluation. Independent t-test, chi-square, ANCOVA, and Pearson's correlation were used in the statistical analysis.

Results

There was statistically significant reduction of RNFL thickness in average (adjusted mean 88.87µm; 95% CI = 86.36, 91.38 vs 94.82µm; 95% CI = 92.32, 97.33; *P* = 0.001), superior (adjusted mean 110.08µm; 95% CI = 106.07, 114.09 vs 119.10µm; 95% CI = 115.09, 123.11; *P* = 0.002) and temporal (adjusted mean 63.77µm; 95% CI = 60.64, 66.90 vs 70.36µm; 95% CI = 67.23, 73.49; *P* = 0.004) in PD group compared to controls. There was significant reduction of central subfoveal CT (adjusted mean 271.13µm; 95% CI = 264.67, 277.60 vs 285.10µm; 95% CI = 278.63, 291.56; *P* = 0.003) in PD group compared to controls. There was significant weak negative correlation between the duration of PD with average RNFL thickness in PD patients (*r* = -0.354, *P* = 0.027). There was significant moderate negative correlation between the duration of PD with central subfoveal CT in PD patients (*r* = -0.493, *P* = 0.001), and weak negative correlation between the stage of PD with central subfoveal CT in PD patients (*r* = -0.380, *P* = 0.017).

Conclusion

The mean of average, superior and temporal RNFL thickness and CT was significantly lower in PD group than controls.

Keywords

Parkinson Disease, retinal nerve fibre layer thickness, choroidal thickness, correlation, optical coherent tomography, neurodegenerative disease

CHAPTER 1:

INTRODUCTION

1.1 PARKINSON DISEASE

Parkinson Disease (PD) is a complex disease and the second most common neurodegenerative disorder after Alzheimer Disease (Kalia, 2015). It was first described by James Parkinson in his "Essay on the shaking palsy" in 1817 (Parkinson, 2002). PD is primarily a motor syndrome with four cardinal signs of resting tremor, rigidity, bradykinesia, and postural instability (Jankovic, 2008). However, 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, 2015). Visual symptoms are also part of the non-motor manifestations, including reduced contrast sensitivity, reduced colour vision, convergence insufficiency, and reading difficulty (Nowacka, 2014).

1.1.1 Prevalence of PD

PD affects 1–2 per 1000 of the population and affects about 1% of people over 60 years of age (Tysnes, 2017). The prevalence of PD rises with age, reaching up to 5 – 10 folds in those over 60 years old (Simon, 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 (GBD 2016 Parkinson's Disease Collaborators, 2018)(Dorsey, 2018). The Malaysian Parkinson's Disease Association estimated about 15,000 to 20,000 PD patients in Malaysia (Bexci, 2018).

1.1.2 Pathogenesis of PD

The pathogenesis of PD is the degeneration of dopaminergic neurons in the substantia nigra and loss of their axons in the nigrostriatal pathway, with the presence of α-synuclein containing Lewy bodies as the pathological feature (MacMahon, 2021). 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, 2020).

1.1.3 Diagnosis of PD

Currently, PD is a clinical diagnosis and there is no test to make a conclusive diagnosis (2012 Consensus Guidelines for the Treatment of Parkinson's Disease, 2012). PD can be further categorised into different Hoehn and Yahr severity staging according to the sides of involvement and severity of motor symptoms (Table 1).

Stage	Involvement	Disability
1	Unilateral	None or minimal
2	Bilateral / midline	Without impairment of balance
3	Bilateral	Mild to moderate Physically independent
4	Bilateral	Severe Able to walk or stand unassisted
5	Bilateral	Confinement to bed or wheelchair unless aided

Table 1: Hoehn and Yahr Staging of PD.

1.2 RETINAL NERVE FIBRE LAYER (RNFL) AND PD

RNFL is one of the retinal layers containing the non-myelinated fibres of retinal ganglion cells, where they are packed together to form the optic nerve and continue posteriorly to form the optic chiasm and optic tract. Lesions that cause the loss of RNFL are detected by examination of the fundus for any optic disc pallor or excavation, as well as using validated test by Optical Coherence Tomography (OCT), an ocular imaging technology that provides non-invasive, rapid, objective, and reproducible measurements of RNFL (Sen, 2014).

Multiple studies have been done to measure the changes in the retina in PD but have shown different results. The studies that measured the 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 the RNFL in the PD group compared to normal controls, including studies by Garcia-Martin et al., Moschos et al., Kaur et al., and etc (Huang, 2021)(Garcia-Martin, 2014)(Moschos, 2018)(Kaur, 2015). In contrast, Tsironi et al. and Nowacka et al. did not observe any significant differences in the RNFL thickness in PD group and normal controls (Tsironi, 2012)(Nowacka, 2015).

1.3 CHOROID AND PD

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, 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, 2015). With the development of technology, optical coherence tomography (OCT) allows 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, 2010).

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

1.4 RATIONALE OF STUDY

The pathognomonic change in PD, namely the dopamine deficit, can affect the retina which contains dopaminergic neurons by causing retinal ganglion cells loss and thus retinal nerve fibre damage. The measurement of RNFL thickness and CT provides an objective morphological assessment of the retina and the choroid. Furthermore, both tests are non-invasive. However, previous studies have not been able to reproduce the similar changes.

So far, there is no single test to reliably diagnose PD (2012 Consensus Guidelines for the Treatment of Parkinson's Disease, 2012). As previous studies have showed, visual symptoms are common among PD patients and could be presented in early stage of PD.

By using OCT in this study, we will be able to objectively measure the damage of dopaminergic neuronal loss in the retina in PD patients by comparing their RNFL thickness and identify the anatomical changes of CT in PD patients compared to that of the control group. As PD is a neurodegenerative disease and retina functions are dependent on choroid, study on the changes in the RNFL thickness and CT could provide potential evidence-based parameters to help to support the diagnosis PD especially in the early stage of PD, and to help to monitor the disease progression.

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CHAPTER 2:

STUDY OBJECTIVES

2.1 General objective

To evaluate the RNFL thickness and CT in PD patients

2.2 Specific Objective

1. To compare the RNFL thickness between PD patients and normal controls
2. To compare the CT between PD patients and normal controls

CHAPTER 3:

MANUSCRIPT

EVALUATION OF RETINAL NERVE FIBRE LAYER THICKNESS AND CHOROIDAL THICKNESS IN PARKINSON DISEASE PATIENTS

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ABSTRACT

Objective: To evaluate the retinal nerve fibre layer (RNFL) thickness and choroidal thickness (CT) in Parkinson Disease (PD) patients. **Methods:** A comparative cross-sectional, hospital-based study. There were 39 PD subjects and 39 controls recruited. These 2 groups were gender and age matched. Subjects that fulfilled the inclusion criteria underwent optical coherence tomography (OCT) for evaluation of RNFL thickness and CT. **Results:** There was statistically significant reduction of RNFL thickness in average (adjusted mean 88.87µm; 95% CI = 86.36, 91.38 vs 94.82µm; 95% CI = 92.32, 97.33; *P* = 0.001), superior (adjusted mean 110.08µm; 95% CI = 106.07, 114.09 vs 119.10µm; 95% CI = 115.09, 123.11; *P* = 0.002) and temporal (adjusted mean 63.77µm; 95% CI = 60.64, 66.90 vs 70.36µm; 95% CI = 67.23, 73.49; *P* = 0.004) in PD group compared to controls. There was significant reduction of central subfoveal CT (adjusted mean 271.13µm; 95% CI = 264.67, 277.60 vs 285.10µm; 95% CI = 278.63, 291.56; *P* = 0.003) in PD group compared to controls. There was significant weak negative correlation between the duration of PD with average RNFL thickness in PD patients (*r* = -0.354, *P* = 0.027). There was significant moderate negative correlation between the duration of PD with central subfoveal CT in PD patients (*r* = -0.493, *P* = 0.001), and weak negative correlation between the stage of PD with central subfoveal CT in PD patients (*r* = -0.380, *P* = 0.017). **Conclusion:** The mean of average, superior and temporal RNFL thickness and CT was significantly lower in PD group than controls.

Keywords: Parkinson Disease, retinal nerve fibre layer thickness, choroidal thickness, correlation, optical coherence tomography, neurodegenerative disease

INTRODUCTION

Parkinson Disease (PD) is a complex disease and the second most common neurodegenerative disorder after Alzheimer Disease [1]. It was first described by James Parkinson in his "Essay on the shaking palsy" in 1817 [2]. It affects one to two per 1000 of the population and affects about 1% of people over 60 years of age [3]. PD prevalence increases with age and up to five to ten folds in those over 60 years old [4]. 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 [5, 6]. The Malaysian Parkinson's Disease Association estimated about 15,000 to 20,000 PD patients in Malaysia [7].

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 [8]. PD is primarily a motor syndrome with four cardinal signs of resting tremor, rigidity, bradykinesia, and postural instability [9]. 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 [9, 10]. Visual symptoms are also part of the non-motor manifestations, including reduced contrast sensitivity, reduced

colour vision, convergence insufficiency, and reading difficulty [11]. Abd Hamid et al. observed a statistically significant reduction of visual acuity in PD patients compared to normal controls [12]. 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 [13].

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., Moschos et al., Kaur et al., and etc [14-17]. In contrast, Tsironi et al. and Nowacka et al. did not observe any significant differences of RNFL thickness in PD group and normal controls [18, 19].

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 [20]. 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 [21]. 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) [22].

To date, the few available studies on CT in PD have shown contrasting results. Moschos et al. and Eraslan et al. reported significant reduction of CT in PD, but Oktem et al. demonstrated the opposite finding with significant increment of CT in PD [16, 23, 24]. Meanwhile, Robbins et al. did not observe any significant difference of CT in PD and normal controls [25].

Currently, PD is a clinical diagnosis and there is no test to make a conclusive diagnosis [26]. 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.

MATERIALS 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. and Moschos et al [16, 27]. 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 100x 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 t-test and Pearson Chi-Square test were used to analyse the demographic data. Independent t-test was used to compare 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.

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

RESULTS

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 Chi-square test, * $P < 0.05$ significant