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WORD COUNT	3779	TIME SUBMITTED	19-JAN-2025 09:32PM
		PAPER ID	114134351

AMPH
AMALTEA MEDICAL PUBLISHING HOUSE
https://medscience.center/journals/

TYPE OF ARTICLE: Original Article

Words count – 3,776

Retinal nerve fiber layer thickness and its correlation with Parkinson's disease severity

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ABSTRACT

Background and Objectives. Parkinson's disease (PD) is a neurodegenerative disorder characterized by a reduction in dopamine levels in the brain and brainstem. Furthermore, dopamine is also found in the ganglion cell area of the Retina Nerve Fiber Layer (RNFL). Thus, the total retinal thickness may be impacted by the dopamine decline in Parkinson's disease. The Parkinson's Disease Composite Scale (PDCS) is a highly reliable and fast tool for measuring the severity of symptoms experienced by individuals with Parkinson's disease (PD). The purpose of this study was to ascertain whether PD severity and RNFL thickness were correlated.

Materials and Methods. A cross-sectional study with 25 PD patients was conducted. PDCS-based severity assessment was recorded (including aspects related to disability, non-motor and motor symptoms, and drug complications). RNFL thickness was measured using Optical Coherence Tomography (OCT) and results were divided into areas of Temporal-Superior, Nasal-Superior, Temporal-Nasal, Temporal-Inferior, Nasal-Inferior, and Global quadrants.

Results. There was a significant negative correlation between PD severity and RNFL thickness in the nasal-superior quadrant ($p = 0.0224$; $r = -0.4547$). Significant negative correlations were also found between the nasal-superior quadrant and the motor ($p = 0.0326$; $r = -0.4285$), non-motor ($p = 0.0081$; $r = -0.5172$), and disability aspects ($p = 0.0293$; $r = -0.4361$).

Conclusions. PD severity increases with RNFL thinning, particularly in the nasal-superior quadrant.

Keywords: RNFL, PDCS, PD, OCT, Dopamine

Abbreviations:

PD : Parkinson's disease
RNFL : Retina Nerve Fiber Layer
PDCS : Parkinson's Disease Composite Scale
OCT : Optical Coherence Tomography
TS : Temporal-Superior
NS : Nasal-Superior
T : Temporal
N : Nasal
TI : Temporal-Inferior
NI : Nasal-Inferior
G : Global
QOL : Quality of Life

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by bradykinesia, tremor, rigidity, and postural instability. The prevalence is about 0,3% and the incidence is 8-18/100.000 population per year which increase with age [1]. In PD, the pathogenic lesion consists of a loss of dopaminergic cell clusters in the brainstem and pigmented neurons in the substantia nigra [2].

Cognitive dysfunction is a common and debilitating non-motor symptom in PD. One of the indicators of cognitive deterioration in PD is visual impairment, including visual hallucinations [1,3]. Dopamine is thought to play a role in this mechanism. Besides being present in the substantia nigra which is the basic pathophysiology of PD, dopamine is also found in the retina. In the retina, dopamine is crucial for processing visual information. Previous studies has revealed that accumulation of α-synuclein in retinal cells causes the retina to gradually degenerate in PD [4]. This could be related to the severity of the disease in PD [5].

Retinal thickness measurement can yield metrics to differentiate between individuals with neurodegenerative disorders, such as PD, and healthy individuals. In fact, previous studies have shown that PD patients have thinner Retinal Nerve Fiber Layer (RNFL) than healthy patients [6]. Optical coherence tomography (OCT) divides the retina into quadrants in order to measure the thickness of the RNFL [5]. This could lead to the possible use of RNFL thickness as a clinical marker for Parkinson's disease assessment and possibly for early detection of deterioration/prognosis [2,6].

The Parkinson's Disease Composite Scale (PDCS) is a parameter that measures the severity of symptoms experienced by patients with PD in a timely manner. It integrates motor, non-motor, medication-related complications, and disability aspects. Designed to complement existing scales, the PDCS is simple and relatively quick to use [7].

The purpose of this study is to evaluate the correlation between PD severity and RNFL thickness. We expect that this information will be taken into account in order to use RNFL thickness as a biomarker to determine the severity of PD.

MATERIALS AND METHODS

Study Design

This cross-sectional study was carried out at Hasanuddin University Hospital Makassar and Dr. Wahidin Sudirohusodo General Hospital. We recruited PD patients ranging in age from 40 to 80, with no prior history of diabetes mellitus, glaucoma, autoimmune diseases, central nervous system infections, or trauma. All subjects were recruited following provision of informed consent.

PDCS Examination

PD patients were evaluated using the PDCS scoring system, which consists of 17 questions with a maximum total score of 68 and is broken down into 4 main categories: motor, non-motor, treatment complications, and disability. After adding up all of the scores, the interpretation is separated into three severity categories: mild (0–23), moderate (24–41), and severe (≥42) [7].

RNFL Examination

RNFL thickness were measured by optical coherence tomography with Heidelberg Engineering (HRA+OCT Spectralis). The measurement of retinal thickness was performed in Temporal-Superior (TS), Nasal-Superior (NS), Temporal (T), Nasal (N), Temporal-Inferior (TI), Nasal-Inferior (NI), and Global (G) quadrants, all depicted in the µm nit. The OCT device's computer-generated computations resulted in the classification of RNFL thickness in each quadrant as normal, borderline, or abnormal.

Statistical analysis

To analyze the data, Graphpad Prism v9 was used. The format for numerical data is mean ± standard deviation. The collected data were subjected to Pearson's correlation test to determine the correlation between RNFL thickness and PD severity. A p value of < 0.05 was considered statistically significant in the analysis.

Ethical approval

Prior to commencement, the study was approved by the health research ethics committee of the Faculty of Medicine, Hasanuddin University Makassar with registration number 24/UN4.6.4.5.31/PP34/2024.

RESULTS

Sample characteristics

A total of 25 PD patients were recruited in the study, consisting of 12 males (48%) and 13 females (52%). The average age of the subjects in this study was 63.68 ± 11.15. In this study, mild severity was found in 15 patients (60%), moderate severity in 10 patients (40%). The average thickness of the RNFL in each quadrant is as follows: Global (G) 107.0 ± 19.70 µm, Temporal-Superior (TS) 139.7 ± 30.18 µm, Nasal-Superior (NS) 115.1 ± 26.28 µm, Nasal (N) 80.78 ± 23.99 µm, Nasal-Inferior (NI) 118.3 ± 32.76 µm, Temporal-Inferior (TI) 151.1 ± 27.17 µm, and Temporal (T) 79.68 ± 16.25 µm.

TABLE 1. Sample characteristics

Variable	Results
Gender (Male/Female)	12/13
Age (Mean Years ± SD)	63.68 ± 11.15
PDCS Severity n(%)	
Mild	15 (60%)
Moderate	10 (40%)
Severe	0 (0%)
RNFL (µm, Mean ± SD)	
Global	107.0 ± 19.70
Temporal-Superior	139.7 ± 30.18
Nasal-Superior	115.1 ± 26.28
Nasal	80.78 ± 23.99
Nasal-Inferior	118.3 ± 32.76
Temporal-Inferior	151.1 ± 27.17
Temporal	79.68 ± 16.25

Correlation between RNFL thickness and overall severity of PD

There was a significant negative correlation of moderate strength between RNFL thickness in the Nasal-Superior quadrant and PD overall severity as measured by the PDCS instrument ($p = 0.0224$; $r = -0.4547$, Pearson's correlation test), as shown in Table 2 and Figure 1A. Therefore, it may be concluded that PD severity will increase proportionately with RNFL thinning in the Nasal-Superior quadrant.

Correlation between RNFL thickness with severity sub-groups

When testing the relationship between motor severity and RNFL thickness (Table 2, Figure 1B) we found a significantly strong negative correlation between the motor component of the PDCS and the RNFL thickness of the Nasal-Superior quadrant ($r = -0.4285$; $p = 0.0326$). Therefore, it may be concluded that the severity of motor symptoms in Parkinson's disease (PD), including bradykinesia, tremor, gait, freezing, postural instability, and nocturnal akinesia, shows a linear increase with thinning of the RNFL in the Nasal-Superior quadrant.

In the non-motor symptom domain (Table 2, Figure 1C) we found a significantly strong negative correlation with RNFL thickness within the Global ($r = 0.4815$; $p = 0.0148$), Nasal-Superior ($r = -0.5172$; $p = 0.0081$), and Nasal ($r = -0.4126$; $p = 0.0404$) quadrants . It was observed that the Nasal-Superior quadrant had a more pronounced negative association. Therefore, it may be concluded that the severity of non-motor symptoms in Parkinson's disease (PD), such as fatigue, urinary problems, cognitive impairment, depression, orthostatic hypotension, and hallucinations, are more pronounced in subjects with thinner RNFL's in the Global, Nasal-Superior, and Nasal quadrants.

Correlation between RNFL thickness and severity of PD treatment complications

Meanwhile, the drug complication component of the PDCS showed no significant correlation with RNFL thickness in all quadrants. When using PDCS to determine the severity of Parkinson's disease based on medication-related complications, there is no correlation between the outcomes of RNFL measures across all quadrants. For the last PDCS domain (Table 2, Figure 1D) we observed a strong negative correlation between the RNFL thickness of the Nasal-Superior

quadrant and patient disability (r = -0.4361; p = 0.0293). Thus, it may be concluded that the degree of impairment in Parkinson's disease (PD) will rise in direct proportion to the thinning of RNFL in the Nasal-Superior quadrant.

TABLE 2. Correlation between severity and RNFL quadrants using pearson test

RNFL	PDCS		Motoric		Non-Motoric		Treatment Complication		Disability	
	r	p	r	p	r	p	r	p	r	p
G	-0.3891	0.0546	-0.3022	0.1421	-0.4815	0.0148*	-0.3391	0.0972	-0.3019	0.1424
TS	-0.2742	0.1846	-0.2123	0.3084	-0.3867	0.0562	-0.1894	0.3646	-0.1735	0.4068
NS	-0.4547	0.0224*	-0.4285	0.0326*	-0.5172	0.0081*	-0.3211	0.1176	-0.4361	0.0293*
N	-0.3135	0.127	-0.2552	0.2183	-0.4126	0.0404*	-0.2439	0.24	-0.2296	0.2697
NI	-0.359	0.078	-0.2882	0.1624	-0.3521	0.0843	-0.3373	0.0992	-0.2933	0.1547
TI	-0.2428	0.2421	-0.1087	0.605	-0.2796	0.1759	-0.3042	0.1392	-0.181	0.3867
T	-0.0754	0.7201	-0.0275	0.8958	-0.1377	0.5116	-0.0975	0.6426	-0.0406	0.8469

*Significant correlation $p < 0.05$, Pearson's correlation test

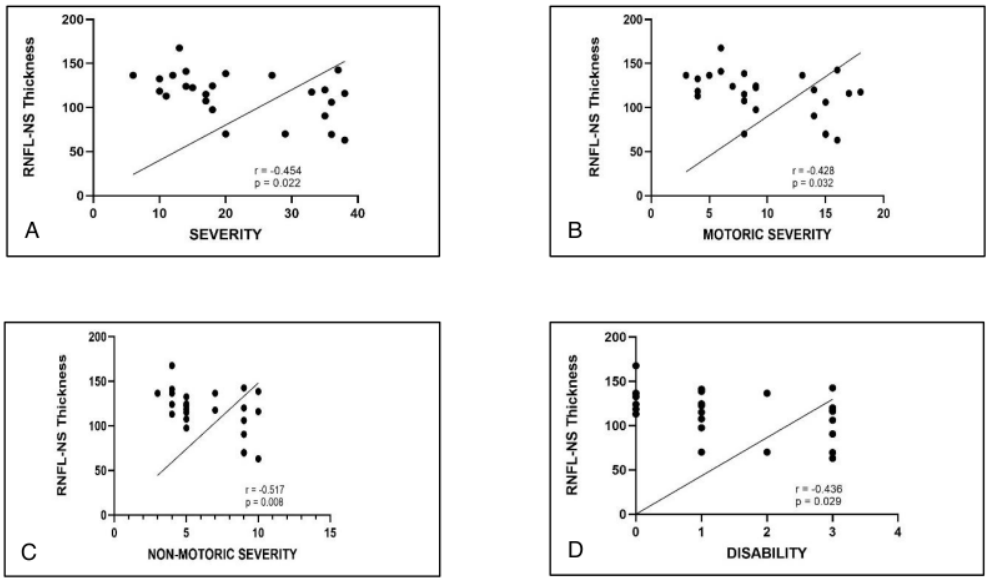

FIGURE 1. Scatterplots displaying the correlations between PDCS severity and the RNFL-NS, (A) Correlation between PDCS severity and RNFL-NS; (B) Correlation between motoric severity and RNFL-NS; (C) Correlation between non-motoric severity and RNFL-NS; (D) Correlation between disability and RNFL-NS; p values were obtained from Pearson's test.

DISCUSSION

In this study, the patient group's average age was 63.68 ± 11.15 years. According to studies done on 100 patients by Satue et al., the average age of PD patients was 64 years [8]. Overall, there was a relatively small gender difference (12 males, 13 females). Hamid et al. found a similar pattern with an average age of 62.0 ± 8.56 years (male: 65, female: 63) [9].

We reported a significant negative correlation between the RNFL thickness and the PD severity score determined using the PDCS tool. The Nasal-Superior quadrant was found to be the location with the strongest correlation. This finding resonates with a study on 55 PD patients by Vishnu et al., who also found a strong negative correlation between RNFL thickness and state of Parkinson's disease, although in said study, the Hoen & Yahr severity rating and UPDRS were used instead of PDCS. The study found that the temporal, superior, inferior, and nasal quadrants all exhibited a strong correlation with PD severity [10]. Similar findings were also observed Hamid et al, wherein 64 PD patients had RNFL thinning, particularly in the superior and inferior quadrants [9].

However, other studies have also implicated other regions of importance. El-Kattan et al reported that RNFL quadrants in the nasal and temporal areas showed a substantial association with the severity of PD [11]. The Temporal-Superior and Temporal-Inferior quadrants were shown to have large regions of RNFL thinning, which was previously also observed in a study by Satue et al. In addition, studies have also demonstrated the simultaneous significance of all quadrants in PD severity. In Yu et al.'s meta-analysis of 13 publications, it was revealed that the thickness of each quadrant of the RNFL might drastically decrease and has a negative correlation with the severity of PD [12]. A study by Jimenez et al. on 52 patients also revealed RNFL thinning in all four PD patient quadrants and demonstrated a strong inverse correlation between PD severity and this RNFL thinning [13].

Further analysis on the relationship between RNFL and the PDCS subgroups also revealed meaningful associations. In this study, there was a strong negative correlation between RNFL thickness and the degree of motor features and disability, particularly in the Nasal-Superior quadrant. This is comparable to the Takwa et al. case control study on 20 PD patients, which demonstrated a negative correlation between RNFL thinning, particularly in the superior quadrant, and PD patients' reduced mobility [14]. RNFL thickness and Motor symptoms of PD patients were shown to be significantly correlated in a study by Vishnu et al, although in this investigation, the RNFL's inferior quadrant had the highest significance [10].

The Nasal-Superior, Nasal, and Global quadrants showed a strong negative correlation in the Non-Motor Severity part of this study as well. Non-motor aspects of PDCS include urinary disorders, cognitive impairment, depression, orthostatic hypotension, and hallucinations. According to studies by Takwa et al., there is a substantial correlation between cognitive decline in patients with PD and RNFL thinning in the superior quadrant [14]. Ramos et al. found that significant thinning of the interplexiform layer is particularly prevalent in PD patients who have visual hallucinations [21]. Conversely, Chang et al. reported that the thickness of the RNFL in the inferior and temporal regions specifically decreases in PD patients with cognitive impairment [4]. This highlights different aspects of retinal changes associated with PD, emphasizing the complexity of visual disturbances in this population.

The disability sub-component was also negatively correlated with the Nasal-Superior in this study. According to studies on 153 PD patients by Satue et al., RNFL is negatively associated with functional disability in PD patients, particularly in the Nasal quadrant of sectors 2 and 5 [15]. Research conducted by Elena et al. found a negative correlation between OCT measurements and neurological markers of PD using the Hoehn and Yahr scale, indicating that patients with greater retinal ganglion cell damage tend to exhibit more severe PD symptoms. Additionally, a positive correlation between OCT parameters and the Schwab and England Activities of Daily Living Scale (SE-ADL) suggests that these patients also experience lower quality of life (QOL). So, when

measuring RNFL with OCT, people with PD can be predicted to have a worsening of their symptoms or to experience a decline in their QOL [16].

The RNFL is located between the inner retinal limiting membrane as the basal lamina of Muller cells and the retinal ganglion cell layer. There are various neurodegenerative illnesses that exhibit histopathological alterations in the RNFL. Retinal ganglion cells and their axons have direct communication with the brain due to the retina's same embryological origin, which is why it is thought of as an outpost of the brain outside the inner cavity of the skull [14,17]. Widespread age-related decreases in the visibility of the RNFL happen without the development of localized abnormalities or the selection of a specific fundus region [18].

Dopamine release in the retina is influenced by the amount of incoming light. In the retina, dopamine acts as a primary neurotransmitter or modulator affecting rod vision and mediating retinal adaptation to light. Dopamine is synthesized and released from dopaminergic amacrine cells or interplexiform cells, which are part of the RNFL. It plays a crucial role in regulating several neurochemical systems, including glutamate, GABA, and glycine in the retina. Dopamine can diffuse up to 3 mm, impacting all types of retinal neurons, whether synaptically connected or not [22,23]. Thus, any visual impairment may relate to disrupted dopamine function in the retina.

Dopamine deficiency in the retina, specifically in the bipolar, ganglion, horizontal, and amacrine cells, is linked to PD in addition to the basal ganglia. Harnois and Paolof discovered that the autopsies of eight PD patients showed reduced retinal dopamine levels [19]. Low dopaminergic input in certain ganglion cells causes atrophy of the retinal fibers and abnormal glutamate production [12].

As a neuropathological marker, aberrant accumulation of α-synuclein can cause synaptic consequences, neuronal death, and disruption of dopamine pathways. α-Synuclein is found in the outer plexiform layer of the retina, where it plays a role in cell signaling, membrane fusion, neurotransmitter release, fatty acid binding, and cell proliferation. The normal balance of α-Synuclein is disrupted by protein alterations that occur in PD. Consequently, α-Synuclein exhibits abnormal aggregation, which sets off intercellular transmission and allows α-Synuclein to proliferate into the interplexiform cells that line the inner of the RNFL. The RNFL thinnings a result of dopaminergic cell insufficiency brought on by this α-Synuclein aggregation [20].

The peripapillary RNFL layer gradually becomes thinner as the severity of PD increases. Accordingly, it is possible to use the average peripapillary RNFL thickness determined by OCT as a biomarker to identify the early onset and progression of PD [13]. OCT readings showed a substantial negative connection with the severity and stage of PD, which may point to a potential dopaminergic depletion in the retina that corresponds to dopamine depletion in the basal ganglia [10].

Currently, there are not many studies that use PDCS as an instrument for determining PD severity, even though we believe PDCS is a useful and quick tool for measuring PD severity. As a result, this study may serve as a guide for future research that uses PDCS as a benchmark for determining PD severity. This study may potentially serve as a guide for developing RNFL thickness as a biomarker predictive of the severity of Parkinson's disease. However this study is limited by the relatively sample size, and findings presented need to be validated in larger scale investigations.

CONCLUSION

PD Severity and RNFL thickness, especially in the Nasal-Superior quadrant, show a significant inverse correlation. We conclude that the severity of PD (motor, non-motor, and disability) will rise with decreasing RNFL thickness.

CONFLICT OF INTEREST

Each author declares that there is no conflict of interest.

AUTHOR'S CONTRIBUTIONS

Conceptualization, A.R., A.M., M.A., and G.S.; Methodology, G.S.; Software, A.R.; Validation, A.R., A.M., M.A., G.S., M.B., and B.U; Formal Analysis, A.R.; Investigation, A.R.; Resources, A.R.; Data Curation, A.R.; Writing—Original Draft Preparation, A.R.; Writing—Review and Editing, A.R., A.M., M.A., G.S., M.B., and B.U.; Visualization, A.R.; Supervision, A.R., A.M., M.A., G.S., M.B., and B.U.; Project Administration, A.R.; Funding Acquisition, A.R., A.M., M.A., and G.S. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGEMENTS

We would like to thank the Faculty of Medicine Hasanuddin University, Neurology Department, Ophthalmology Department, staff of Dr. Wahidin Sudirohusodo General Hospital, and staff of Hasanuddin University Hospital Makassar for technical assistance during the study.

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