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ORIGINAL ARTICLE

Ocular and Radiological Biomarkers in Parkinson's Disease: A Case-Control Study

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ABSTRACT

Background: Emerging evidence suggests that ocular and radiological parameters may serve as early indicators of neurological decline in Parkinson's disease (PD). This study aims to compare specific eye-related measurements between individuals with PD and healthy controls and evaluate the correlation between ocular measurements and clinical as well as radiological parameters.

Methods: This case-control study was conducted between February 2022 and September 2023. The study included 22 PD patients and 20 healthy controls. Neurological and ophthalmological evaluations were performed using optical coherence tomography to assess retinal structures. Additionally, magnetic resonance imaging with diffusion tensor imaging was used to measure white matter integrity.

Results: The study enrolled 42 participants, with a predominance of males. Disease severity and cognitive functions were assessed and indicated considerable impairment among PD patients. Ocular and retinal parameters showed differences in retinal nerve fiber layer thickness and choroidal thickness. MRI metrics showed significant reductions in fractional anisotropy and increases in mean diffusivity in several brain regions of PD patients, indicating white matter degeneration. Correlation analyses revealed significant associations between ocular parameters as well as white matter integrity and cognitive impairment.

Conclusion: Our study suggests that degenerative processes in PD extend beyond the central nervous system to involve the eye, with significant retinal neurodegeneration and increased axonal damage compared to healthy controls. Comprehensive assessments combining ocular, neurological, and radiological parameters could improve the understanding and management of PD.

Keywords: Parkinson's Disease; Cognition; Neurodegeneration; Radiology;ophthalmology

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by prominent motor symptoms, including bradykinesia, resting tremor, and rigidity, as well as nonmotor symptoms such as cognitive decline, olfactory dysfunction, anxiety, depression, and visual impairments[1]. These manifestations are primarily due to the degeneration of dopaminergic neurons in the substantia nigra (SN), with aggregation of α-synuclein within neuronal cells [2]. PD affects over 1% of the population aged 65 and older, with projections indicating a doubling of this figure by 2030[3]. Patients with Parkinson's disease have a higher risk of developing dementia than the general population, and cognitive decline is inevitable in many cases [4,5]. While the precise etiology of PD is still unclear, emerging evidence suggests that

cerebral small vessel disease may contribute to its development with a higher incidence of cerebral ischemic lesions [6].

Given that the retina serves as an extension of the central nervous system, it becomes a pivotal indicator of neurological ailments, aiding in their diagnosis and management [7]. Research indicates that the degeneration of dopamine neurons affects the SN and retinal ganglion cells (RGCs) [8]. This observation underscores the potential of ocular assessments in predicting cognitive decline and dementia risks in newly diagnosed PD patients.

METHODS

This case-control study was conducted in Kafrelsheikh University Hospital during the period from February 2022 to September 2023. The study participants were divided into two groups: group 1 consisted of 22 patients diagnosed with PD, and group 2 (controls) comprised 20 healthy individuals. The study adhered to the STROBE Checklist in its entirety [9].

Inclusion criteria encompassed patients with PD of both sexes who met the diagnosis criteria for idiopathic PD according to the Movement Disorder Society (MDS) clinical diagnostic criteria for PD, 2015 [10]. Exclusion criteria involved the presence of significant refractive errors such as high myopia, local ocular diseases such as diabetic retinopathy, media opacification or glaucoma as well as a history of ocular surgery or trauma. Additionally, individuals who refused to participate were excluded.

All patients underwent a comprehensive assessment, which included a detailed medical history, neurological examination by a qualified neurologist, and ophthalmological evaluation conducted by experienced ophthalmologists.

PD diagnosis was established according to established clinical as well as neuroimaging criteria [11]. Age, sex, and PD duration were documented. Motor assessment was meticulously carried out using the Hoehn-Yahr scale as well as the Unified Parkinson Disease Rating Scale part III score (UPDRS III) to evaluate disease severity [12-14]. The Montreal Cognitive Assessment (MoCA) scale was also used to assess the patients' cognitive status [15,16].

Ophthalmological Evaluation and Structural Analysis of the Retina

The ophthalmological evaluation included an examination encompassing pupillary assessment, anterior segment examination, and funduscopic examination. Evaluation of visual function included evaluating best-corrected visual acuity (BCVA) and Intraocular pressure using Goldmann's applanation tonometer (Keeler Itd., Windsor UK). Structural examination of the retina was performed with a spectral domain (SD) OCT, specifically a Cirrus high-definition OCT system (Carl Zeiss Meditec Inc, Dublin, California, USA). This involved three protocols: one for macular thickness, a retinal nerve fiber layer (RNFL) protocol, and a ganglion cell protocol for detailed layer analysis.

Image Acquisition

In the study, MRI scans were conducted using a 3 Tesla Philips Ingenia scanner. The protocol included a 3D T1-weighted sequence with the following settings: matrix size of 256 × 256, a slice thickness of 1.2 mm, a flip angle of 12°, a repetition time (TR) of 7.77 ms, and an echo time (TE) of 2.79 ms. Additionally, diffusion tensor (DT) imaging utilized a single-shot spin-echo EPI sequence with a matrix size of 112 × 112, TR of 13000 ms, TE of 103 ms, and an isotropic voxel size of 2.5 mm. Diffusion gradients were encoded at b values of 0 and 1000 sec/mm².

Moreover, this study employed DTI indices such as fractional anisotropy (FA) and mean diffusivity (MD). FA, a measure ranging from zero to one, quantifies the degree of diffusion anisotropy in tissues, with higher values indicating more intact white matter. MD quantifies the overall water diffusion within brain tissue, typically lower in intact white matter, reflecting diffusion in all directions. Data processing utilized FiberTrak DTI software, incorporating eddy current correction to minimize distortions and artifacts. Diffusion maps were aligned with T1-weighted images for anatomical reference. All data underwent manual analysis using regions of interest (ROI) to measure FA and MD levels in the SN, corpus callosum (CC), and cingulum. The resultant MD and FA maps were then generated, and representative diffusion tensor images are displayed in **Figure 1.**

Ethical Considerations

Prior to participation, written consent was obtained after providing detailed information about the study's objectives and procedures. Privacy and confidentiality were strictly upheld during all phases of the study, from data gathering to analysis. The study received initial approval from the institutional review board committee (IRB number [MKSU 50-5-13]).

Statistical Analysis

We conducted our statistical analysis by encoding, organizing, and processing the data using IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY: IBM Corp). The Shapiro-Wilk test assessed data distribution normality. We reported the median and interquartile range (IQR) for non-parametric data and employed the Mann-Whitney U test (Wilcoxon rank sum test) to evaluate the differences. Dichotomous data were summarized by frequency (count) and percentage, and the Chi-square ($\chi 2$) test was applied for categorical data comparison. We also performed correlation analysis using Spearman's rank correlation coefficient. Statistical significance was set at $p < 0.05$ for all tests.

RESULTS

Sociodemographic characteristics

Our study enrolled a total of 42 participants. The baseline characteristics of the participants are summarized in ***Table 1***. The case and control groups were matched by age and gender.The mean age of cases was 63.8 (6.6) years; mean (SD) and 61.3(4.6) years for controls. About 86.4% of cases and 65.0% of controls were male, resulting in an overall male predominance of 76.2% across the entire cohort (p = 0.104). The disease duration was found to have a mean (SD) of 4.0 (1.6) years among cases, ranging from 1.0 to 7.0 years. Furthermore, assessments of disease severity using the UPDRS revealed a mean (SD) total score of 65.8 (11.8) among cases, indicating a considerable level of impairment. Additionally, the modified scale demonstrated a mean (SD) score of 2.2 (0.9) for cases, with scores ranging from 1.0 to 4.0**.** The median MoCA score was 16 (IQR: 11-20), ***Table S1***. The majority of participants scored very low in the "Abstraction" domain, with 14 out of 22 participants (64%) scoring 0, and 7 out of 22 participants (32%) scoring 1, indicating significant impairment in abstract thinking abilities.

Motor Examination Scores

Regarding the evaluation of motor function using MDS-UPDRS in patients with PD, various motor domains were assessed, and their summary statistics are presented in ***Table S2***. The median scores for motor subscores ranged from 1 to 3, reflecting patients' variability in motor impairment. Subscores for tasks such as finger tapping, hand movements, pronation-supination, toe-tapping, leg agility, arising from a chair, and postural stability demonstrated median scores of 3, indicating moderate impairment. In contrast, subscores for rigidity in various body regions and posture exhibited median scores ranging from 1 to 2, suggesting relatively milder impairment. The total MDS-UPDRS score had a median score of 65, with an IQR of 14.5 (range 41 to 86).

Ocular and retinal parameters

BCVA measurements demonstrated similar values between cases and controls for both the right (Rt) and left (Lt) eyes, with mean values of 0.3-0.4 in both groups (all p>0.05). Assessment of pupil reactivity revealed no abnormalities in either eye of the participants. Similarly, evaluations of the anterior and posterior segments of the eye showed no discernible abnormalities in either group. Intraocular pressure (IOP) measurements were comparable between cases and controls for both the right and left eyes, with mean values ranging from 13.0 to 14 mmHg. Statistical analysis revealed no significant difference in IOP between the two groups for either eye *(Rt IOP: $F_{(1,40)} = 0.06$, $P = 0.80$; Lt IOP: $F_{(1,40)} = 0.07$, $P = 0.79$)*, ***Table S3***.

The total thickness of the right eye RNFL was comparable between cases (median 106.5) and controls (median 107.5) (P=0.58), ***Table S3***. However, significant differences were observed in the superonasal (P=0.01) and inferonasal (P<0.01) quadrants. Similarly, for the left eye, total RNFL thickness did not significantly differ between cases (median 112.5) and controls (median 110.5), P=0.56. However, significant differences were noted in the inferonasal (P=0.04) quadrant. In the left eye, the superonasal quadrant demonstrated thicker measurements in controls (median 136.5) compared to cases (median 128.0), with a p-value of 0.05. Nasal and temporal quadrant thickness showed insignificant differences between groups (all p>0.05).

For the right eye, the median choroidal thickness in the cases group was 219.5 μm, whereas in controls, it measured 288.0 μm. The between-group comparison yielded a statistically significant difference ($p < 0.01$). Similarly, the median choroidal thickness for the left eye was 220.5 μm in cases and 260.5 μm in controls. This disparity also reached statistical significance ($p < 0.01$), suggesting a thinner choroid in cases than in controls in both eyes, ***Table S3***.

Imaging Metrics

Table S4 summarizes fractional anisotropy (FA) and mean diffusivity (MD) across different regions of interest, comparing cases to controls. We observed significant differences between cases and controls across multiple brain regions for FA measurements. In the right cingulate, the median FA values were 0.4 in cases and 0.9 in controls, with a statistically

significant difference. Similarly, in the left cingulate, corpus callosum genu, corpus callosum splenium, and bilateral SN, FA values exhibited statistically significant differences between cases and controls, as evidenced by their respective test statistics ($p < 0.01$). Regarding MD measurements, substantial differences were also observed between cases and controls in various brain regions. For instance, in the right cingulate, the median MD values were 0.8 in cases and 0.4 in controls ($p < 0.01$). Similarly, significant differences were noted in the left cingulate, corpus callosum genu, corpus callosum splenium, and bilateral SN, with all test statistics indicating statistical significance ($p < 0.01$).

Correlation analysis

The correlation analysis of RNFL thickness and cognitive function is shown in ***Table 2***. We observed significant correlations that suggest interrelated patterns in RNFL thickness across different quadrants, emphasizing potential anatomical associations that may be relevant in clinical evaluations involving these measurements.

Table 3 shows the correlations and corresponding p-values between MOCA total scores and DTI metrics in PD patients. We observed significant correlations between MOCA total scores and MD in the corpus callosum genu (Spearman's rho = -0.494, $p = 0.019$), indicating the relationship between cognitive performance and white matter integrity in this region. No other significant correlations were found between MOCA total scores, and the other DTI metrics assessed (all $p > 0.05$).

We found no significant correlation between the RNFL thickness in both eyes and disease severity as assessed by the UPDRS***(Figures 2 and 3).*** Also,we observed no significant correlation between RNFL thickness of both eyes and disease duration ***(Figures S1 and S2).***

Table 1: Demographic and clinical characteristics of the study participants

	Cases (N=22)	Control (N=22)	p-value
Age (year)			0.152
Mean (SD)	63.8(6.6)	61.3 (4.6)	
Range	51.0 - 75.0	50.0 - 73.0	
Gender			0.104
Female	3.0 (13.6%)	7.0 (35.0%)	
Male	19.0 (86.4%)	13.0 (65.0%)	
Duration (year)			
Mean (SD)	4.0 (1.6)	-	
Range	1.0 - 7.0	-	
Total UPDRS score		-	
Mean (SD)	65.8 (11.8)	-	
Range	41.0 - 86.0	-	
Modified scale		-	
Mean (SD)	2.2 (0.9)	-	
Range	1.0 - 4.0	-	

Table 2. Correlation Analysis of Retinal Nerve Fiber Layer Thickness and Cognitive Function in Parkinson's Disease Patients

		MOCA: Total	Rt Total RNFL thickness	Rt Superonasal	Rt Inferonasal	Rt Nasal	Rt Temporal	Lt Total RNFL thickness	Lt Superonasal	Lt Inferonasal	Lt Nasal	Lt Temporal
MOCA: Total	**r**	—										
	p-value	—										
Rt Total RNFL thickness	**r**	0.231	—									
	p-value	0.301	—									
Rt Superonasal	**r**	-0.054	0.366	—								
	p-value	0.811	0.094	—								
Rt Inferonasal	**r**	0.083	0.384	0.598	—							
	p-value	0.715	0.078	0.003	—							
Rt Nasal	**r**	0.004	0.27	0.467	0.336	—						
	p-value	0.987	0.223	0.028	0.126	—						
Rt Temporal	**r**	0.267	0.023	0.111	0.485	0.066	—					
	p-value	0.23	0.92	0.623	0.022	0.77	—					
Lt Total RNFL thickness	**r**	0.153	0.689	0.585	0.584	0.116	0.102	—				
	p-value	0.497	< .001	0.004	0.004	0.607	0.653	—				
Lt Superonasal	**r**	-0.11	0.176	0.733	0.592	0.502	0.042	0.457	—			
	p-value	0.626	0.434	< .001	0.004	0.017	0.851	0.033	—			
Lt Inferonasal	**r**	0.048	0.299	0.663	0.854	0.22	0.464	0.678	0.542	—		
	p-value	0.832	0.176	< .001	< .001	0.326	0.029	< .001	0.009	—		
Lt Nasal	**r**	0.18	0.215	0.462	0.638	0.584	0.356	0.463	0.737	0.574	—	
	p-value	0.423	0.338	0.03	0.001	0.004	0.104	0.03	< .001	0.005	—	
Lt Temporal	**r**	-0.243	-0.229	-0.197	0.116	0.026	0.469	0.127	0.002	0.177	0.106	—
	p-value	0.276	0.305	0.38	0.606	0.908	0.028	0.574	0.993	0.431	0.64	—

Table 3. Correlation Analysis of Montreal Cognitive Assessment total scores and diffusion tensor imaging metrics in Parkinson's Disease Patients

		MOCA: Total	FA Rt Cingulate	FA Lt Cingulate	FA Corpus callosum	FA Corpus callosum splenium	FA Rt Substantia nigra	FA Lt Substantia	MD Rt Cingulate	MD Lt Cingulate	MD Corpus	MD Corpus	MD Rt Substantia	MD Lt Substantia nigra
MOCA: Total	r	—												
	p	—												
FA Rt Cingulate	r	0.01	—											
	p	0.97	—											
FA Lt Cingulate	r	0.24	0.82	—										
	p	0.28	< .001	—										
FA Corpus callosum genu	r	0.21	0.09	0.06	—									
	p	0.36	0.69	0.79	—									
FA Corpus callosum splenium	r	0.13	0.38	0.43	0.60	—								
	p	0.57	0.09	0.05	0.00	—								
FA Rt Substantia nigra	r	0.06	0.12	0.52	0.03	0.34	—							
	p	0.79	0.60	0.01	0.88	0.12	—							
FA Lt Substantia nigra	r	-0.13	0.21	0.45	0.08	0.08	0.77	—						
	p	0.56	0.36	0.04	0.74	0.73	< .001	—						
MD Rt Cingulate	r	-0.22	-0.17	-0.17	-0.22	-0.42	-0.31	-0.22	—					
	p	0.32	0.46	0.45	0.33	0.05	0.16	0.34	—					
MD Lt Cingulate	r	-0.32	-0.29	-0.41	-0.40	-0.70	-0.46	-0.24	0.65	—				
	p	0.15	0.19	0.06	0.07	< .001	0.03	0.29	< .001	—				
MD Corpus callosum genu	r	-0.49	-0.23	-0.33	-0.50	-0.65	-0.11	0.15	0.39	0.64	—			
	p	0.02	0.30	0.13	0.02	0.00	0.63	0.51	0.08	0.00	—			
MD Corpus callosum splenium	r	-0.25	-0.26	-0.38	-0.13	-0.28	-0.36	-0.39	0.50	0.48	0.44	—		
	p	0.26	0.24	0.08	0.55	0.21	0.10	0.07	0.02	0.03	0.04	—		
MD Rt Substantia nigra	r	0.11	0.19	0.27	-0.14	-0.21	0.07	0.19	0.15	0.18	0.30	0.04	—	
	p	0.63	0.40	0.23	0.55	0.34	0.75	0.39	0.51	0.44	0.18	0.87	—	
MD Lt Substantia nigra	r	0.04	0.05	-0.08	-0.25	-0.19	-0.33	-0.30	0.34	0.25	0.10	0.33	0.35	—
	p	0.85	0.82	0.74	0.25	0.40	0.13	0.17	0.12	0.27	0.65	0.14	0.12	—

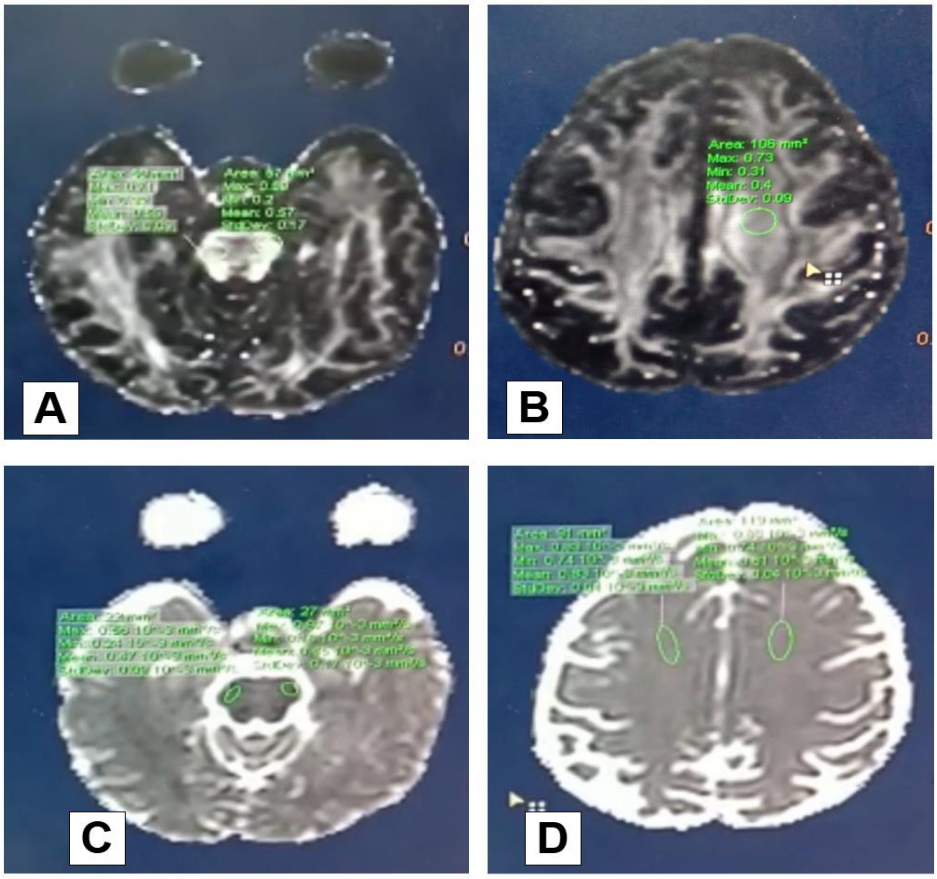

Figure 1: Diffusion Tensor Imaging (DTI) of the Brain. **(A & B)** FA grayscale images with ROI positioned at the substantia nigra (A) and the cingulum (B). **(C & D)** MD grayscale images with ROI at the substantia nigra (C) and the cingulum (D).

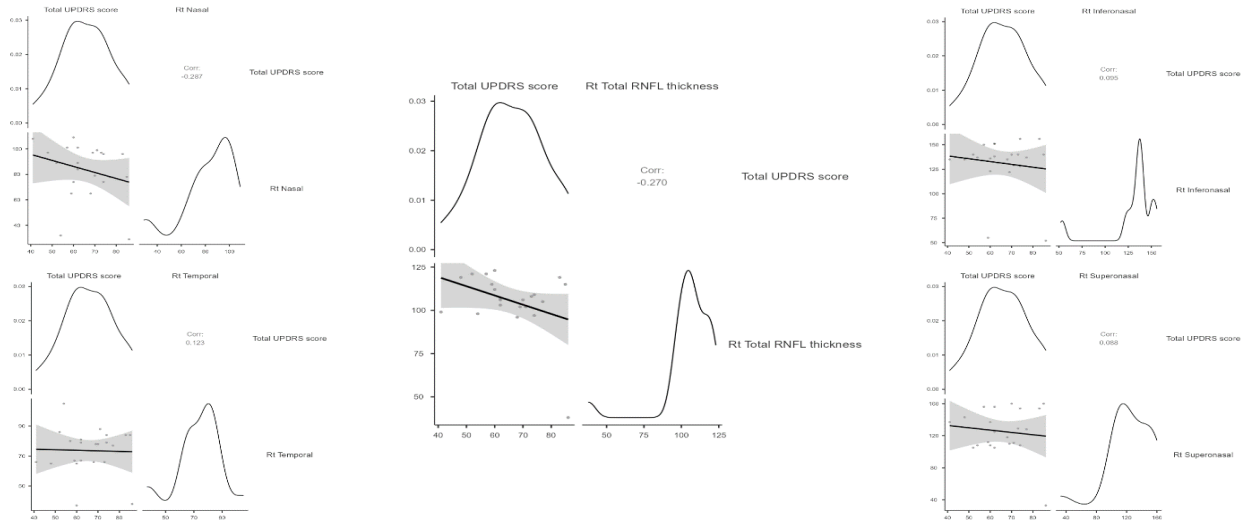

Figure 2 displays the correlation between the right retinal nerve fiber layer (RNFL) thickness and the total UPDRS score.

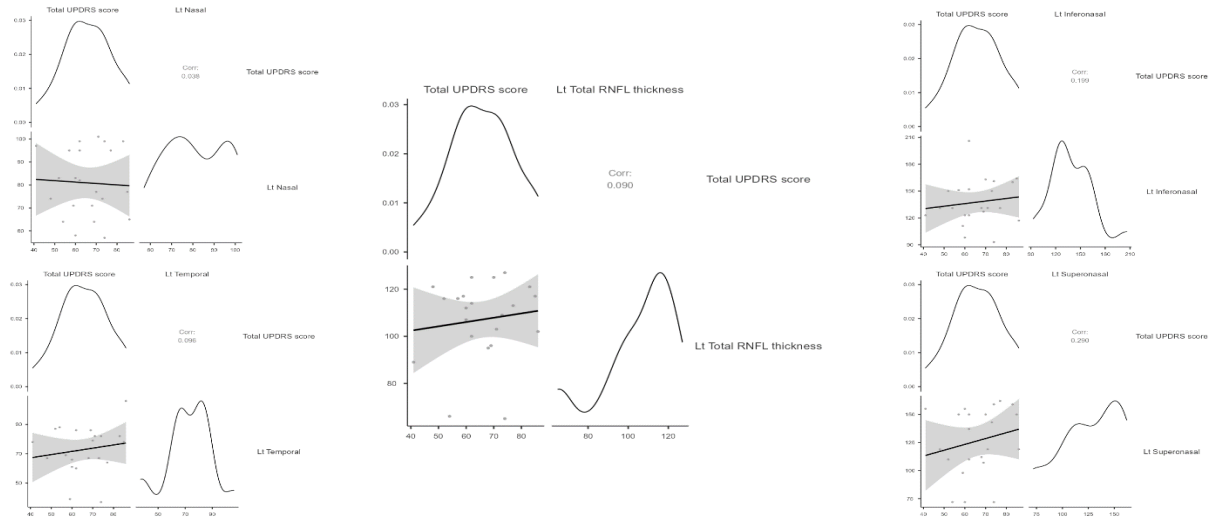

Figure 3 displays the correlation between the left retinal nerve fiber layer (RNFL) thickness and the total UPDRS score.

DISCUSSION

Our investigation aimed to evaluate the correlation between different clinical parameters in individuals with PD, RNF thickness, and white matter integrity. Notably, Our study exhibitsa predominance of males in both groups. Among PD patients, motor function evaluations highlighted variability in impairment across different domains. Despite similar visual acuity and pupil reactivity between PD cases and controls, our analysis revealed differences in specific ocular measurements. While total RNFL thickness did not significantly differ between groups, regional variations in RNFL thickness and thinner choroidal thickness in PD cases were observed. These findings suggest potential ocular manifestations associated with PD pathology. Furthermore, our imaging metrics analysis demonstrated significant differences in FA and MD measurements between PD cases and controls across various brain regions. Lower FA values and higher MD values in cases suggest alterations in white matter integrity, implicating neurodegenerative processes associated with PD [17]. In addition, correlation analysis revealed associations between disease duration, motor impairment severity, and white matter integrity in specific brain regions, highlighting the interplay between clinical parameters and neurological changes in PD progression. Our study underscores the importance of comprehensive assessments encompassing both ocular and neurological parameters to better understand PD pathophysiology and its clinical implications. These findings may inform future research endeavors to elucidate early diagnostic markers and therapeutic targets for PD management.

Current evidence concentrates on identifying early diagnostic markers for PD through non-motor symptoms, neuroimaging, and analysis of body fluids, with a notable focus on retinal structural changes. Research of PD animal models has highlighted that retinal changes, such as swelling and loss of RGCs, occur as early as 20 days after induction. In contrast, characteristic pathological changes in the brain's SN and striatum only manifest around 60 days post-induction [18]. These findings suggest that retinal changes could serve as a more significant indicator for the early detection of PD, occurring before the onset of the disease's typical motor symptoms and evident brain pathology.

The phenomenon of RNFL changes in PD was initially identified by Inzelberg et al. [19]. Subsequent studies have shown varying results, with some confirming RNFL thinning and the loss of RGCs [20,21]. In contrast, others found non significant changes between PD and healthy control despite large sample sizes [22–24]. The accumulation of α-synuclein in PD damages specific subgroups of retinal ganglion cells and non-elongated cells, leading to visual disturbances in PD[25]. The absence of elongated cells disrupts RGC function, significantly contributing to these visual issues. Moreover, substantial retinal thinning, including the thinning of the RNFL, has been reported in patients with PD, independent of drug therapy, as confirmed by a large-sample 2021 meta-analysis [26]. A previous study pointed out that the inner retinal layers are predominantly affected in PD

patients [27]; this finding contrasts with earlier evidence, which suggested that the effects were mainly observed in the inferior and temporal quadrants of the retina [28]. They also found that the thickness of the RGCs layer inversely correlates with the disease's duration and severity, suggesting that GCL thickness can predict axonal damage in PD patients [29]. These progressive changes in the RNFL were documented to be correlated with functional impairments and disease advancement, as gauged by the Hoehn and Yahr (HY) scale [29]. Prior cross-sectional studies have also identified an inverse relationship between HY scores and measurements of macular thickness[22, 28]. From a pathophysiological perspective, recent evidence suggests that as PD progresses, the ongoing loss of dopaminergic neurons may lead to a corresponding decrease in retinal thickness, positioning this as a potential biomarker of neurodegeneration detectable through OCT. This hypothesis is bolstered by several studies that have specifically analyzed changes in retinal thickness by quadrants in patients whose disease duration exceeded ten years. However, the present study found that the disease duration did not impact changes in RNFL thickness. The average duration of the disease among participants was less than ten years (mean 4.0, SD 1.6), possibly explaining the absence of correlation observed in our findings. This aligns with other studies that have also noted a lack of correlation but did not evaluate it with respect to specific retinal quadrants.

From a pathophysiological standpoint, recent data suggests that the continued loss of dopaminergic neurons would subsequently decrease retinal thickness as PD progresses, making this a potential biomarker of neurodegeneration detectable through OCT. Several studies have supported this hypothesis, specifically analyzing retinal thickness changes by quadrants in individuals with a disease duration exceeding 10 years [30- 32]. However, in the present study, it was observed that neither the duration nor the severity of the disease exerted any influence on changes in RNFL thickness**.** The absence of correlation noted in our study aligns with findings from previous OCT research, which found no significant association between RNFL thickness, total macular volume, or intraretinal layer thickness, and either the severity or duration of the disease [33, 34]. While these studies have acknowledged this absence of correlation, they have not examined it in relation to specific retinal quadrants. We did not observe such an association, which may be attributed to the composition of our study population, primarily consisting of PD patients in the early stages, with an average PD duration of <10 years (mean 4.0, SD 1.6). Despite the wealth of information on these structural changes, a few have explored retinal vascular abnormalities in PD patients, indicating a gap in research on this aspect of the disease[35]. Another study suggests that retinal capillary densities are significantly lower in the early PD stages, emphasizing that retinal capillary impairments manifest early in PD, potentially before motor symptoms appear. However, the study found no correlation between the duration or severity of the disease and changes in retinal microvascular densities or intraretinal layer thickness, possibly due to the study's focus on early-stage PD patients. A long-term assessment of both functional visual parameters and changes in RNFL and macular thickness in PD patients highlighted significant reductions in contrast sensitivity and color vision. These changes are attributed to dopamine depletion in the retinas of individuals with PD, which is believed to be the underlying cause of the progressive visual impairments observed in these patients [29]. In the same study, the authors observed a link between progressive changes in the retina and the progression of PD. The evaluation of PD progression in the study relied exclusively on the Hoehn and Yahr scale. Patients with more severe impairments, evidenced by worse HY scores and rapid disease progression, were excluded from the final analysis because they could not complete the tests. This exclusion might have led to an underestimation of the relationship between disease severity and retinal thinning.

Regarding macular measurements, evidence has yielded inconsistent findings; some studies report a significant reduction in macular volume in PD patients [21, 34,35], while others found no notable differences between patients and controls [22, 23]. Conflicting results across studies may arise from variables like participant selection, limited sample sizes, or variations in the sensitivity of OCT devices. In a 5-year longitudinal study, no significant differences in macular thickness were initially detected between PD patients and controls[36],. However, a notable progressive thinning in the macular region was observed in PD subjects over the study period. This progression suggests continuous retinal changes in PD patients, indicating a gradual degenerative process even in the absence of initial disparities.

FA is a key metric used in DTI to assess the integrity of white matter tracts in the brain. Research has

explored FA differences between PD patients and healthy individuals. A study identified significant reductions in FA in various brain regions of individuals with PD and mild cognitive impairment rather than cognitively normal individuals with PD, as well as healthy controls. This suggests that FA might be a viable biomarker for detecting early cognitive decline in PD[37]. Zhang et al. demonstrated that individuals with PD exhibit reduced FA values in the cerebellar white matter and orbitofrontal cortex, which correlated with olfactory dysfunction. This highlights the potential of FA in identifying specific brain regions affected by PD and linking these changes to clinical symptoms [38]. Similarly, Aquino et al. reported that FA values in the SN were significantly lower in advanced stages of PD compared to early stages and controls, indicating that FA measurements can reflect disease progression [39]. However, the stability and reliability of FA as a biomarker are still under scrutiny. Schwarz et al. found inconsistent results in FA measurements across different studies, questioning its utility as a standalone diagnostic tool for PD [40]. Their meta-analysis revealed significant variability, suggesting that additional diffusion measures might be necessary to improve diagnostic accuracy.

MD measures the average rate of water diffusion within tissue and provides insights into tissue density and integrity. Elevated MD values typically indicate tissue damage or loss of structural integrity. A study reported significant increases in MD in PD patients with mild cognitive impairment compared to healthy controls, suggesting that MD could help identify early neurodegenerative PD changes [36]. Aquino et al. observed increased MD values in the SN of PD patients, which correlated with disease severity. This supports the use of MD as a marker for tracking the progression of PD and assessing the extent of neural damage in specific brain regions [39]. Additionally, Lenfeldt et al. (2017) found that MD values in the striatum negatively correlated with dopamine transporter (DAT) uptake, indicating that increased MD may reflect dopaminergic degeneration in PD [41]. Bergamino et al. highlighted the presence of widespread microstructural damage in the frontal and parietal white matter of early-stage PD patients, evidenced by increased MD values[42]. These findings suggest that MD could be useful in detecting early changes in white matter integrity even before significant clinical symptoms manifest. Based on this, both FA and MD are valuable metrics in DTI studies of PD, offering insights into the structural changes associated with the disease. While FA reductions highlight regions of impaired white matter integrity, increased MD values indicate tissue damage and degeneration. Together, these measures provide a comprehensive picture of the microstructural alterations in PD, although their variability suggests a need for complementary imaging techniques to enhance diagnostic precision.

Our study had some limitations, notably including both eyes of each participant in the analysis. This approach can be contentious as it might mask subtle symmetrical changes in the eyes, introducing a degree of dependency in the measurements. However, research suggests that retinal involvement in PD patients can be asymmetrical [43], supporting the inclusion of both eyes in analyses. Additionally, using data from both eyes typically carries minimal risk, even if there is no correlation between the eyes. Another limitation not addressed in our study is the inability to use comprehensive color assessments, which are essential for a detailed evaluation of color vision changes in patients with PD. We recommend the utilization of OCT-angiography in future studies as a non-invasive method for excluding optic disc ischemic pathology. Additionally, we suggest employing corneal thickness measurement via pachymetry to exclude patients with normotensive or hypotensive glaucoma, as those with thin corneas may exhibit falsely normal intraocular pressure readings when assessed with an applanation tonometer.

Conclusion: Our study suggests that the degenerative processes in patients with PD extend beyond the central nervous system to involve the eye. Compared with healthy controls, those patients experience significant retinal neurodegeneration, evidenced by increased axonal damage. Assessing this damage by measuring the thickness of the RNFL and RGCs via OCT has proven to be a pivotal method.

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SUPPLEMENTARY DATA

Table S1: Motor Examination Scores in Patients with Parkinson's Disease

MDS-UPDRS motor	N	Mean	SE	Lower 95% CI	Upper 95% CI	Median	SD	IQR
Speech	22	1.68	0.102	1.47	1.89	2	0.477	1
Facial expression	22	2.55	0.109	2.319	2.77	3	0.51	1
Rigidity, neck	22	1.59	0.157	1.265	1.92	2	0.734	0.75
Rigidity, right upper extremity	22	2.09	0.13	1.82	2.36	2	0.61	0
Rigidity, left upper extremity	22	1.91	0.13	1.639	2.18	2	0.61	0
Rigidity, right lower extremity	22	1.45	0.171	1.1	1.81	1	0.8	1
Rigidity, left lower extremity	22	1.36	0.192	0.964	1.76	1	0.902	1
Finger tapping—right hand	22	2.82	0.125	2.557	3.08	3	0.588	0.75
Finger tapping—left hand	22	2.5	0.143	2.202	2.8	2.5	0.673	1
Hand movements—right hand	22	2.82	0.125	2.557	3.08	3	0.588	0.75
Hand movements—left hand	22	2.5	0.143	2.202	2.8	2.5	0.673	1
Pronation-supination—right hand	22	2.82	0.125	2.557	3.08	3	0.588	0.75
Pronation-supination—left hand	22	2.5	0.143	2.202	2.8	2.5	0.673	1
Toe-tapping—right foot	22	2.82	0.125	2.557	3.08	3	0.588	0.75
Toe-tapping—left foot	22	2.5	0.143	2.202	2.8	2.5	0.673	1
Leg agility—right leg	22	2.82	0.125	2.557	3.08	3	0.588	0.75
Leg agility—left leg	22	2.5	0.143	2.202	2.8	2.5	0.673	1
Arising from chair	22	2.91	0.16	2.576	3.24	3	0.75	1
Gait	22	2.36	0.124	2.106	2.62	2	0.581	1
Freezing of gait	22	2.14	0.151	1.821	2.45	2	0.71	1
Postural stability	22	2.23	0.146	1.923	2.53	2	0.685	1
Posture	22	1.55	0.109	1.319	1.77	2	0.51	1
Body bradykinesia	22	2.18	0.142	1.887	2.48	2	0.664	1
Postural tremor—right hand	22	2.82	0.125	2.557	3.08	3	0.588	0.75
Postural tremor—left hand	22	2.5	0.143	2.202	2.8	2.5	0.673	1
Kinetic tremor—right hand	22	2.82	0.125	2.557	3.08	3	0.588	0.75
Kinetic tremor—left hand	22	2.5	0.143	2.202	2.8	2.5	0.673	1
Constancy of rest tremor	22	2.55	0.109	2.319	2.77	3	0.51	1
Total UPDRS score	22	65.77	2.523	60.527	71.02	65	11.832	14.5

Table S2: Montreal Cognitive Assessment Scores in Participants with Parkinson's Disease

Montreal Cognitive Assessment (MoCA)	N = 22
Visuospatial/Executive	
0	3 (14%)
1	9 (41%)
2	6 (27%)
3	2 (9.1%)
4	1 (4.5%)
5	1 (4.5%)
Naming	
1	5 (23%)
2	2 (9.1%)

Montreal Cognitive Assessment (MoCA)	**N = 22**
3	15 (68%)
Attention	
1	2 (9.1%)
2	5 (23%)
4	5 (23%)
5	5 (23%)
6	5 (23%)
Language	
0	2 (9.1%)
1	10 (45%)
2	5 (23%)
3	5 (23%)
Abstraction	
0	14 (64%)
1	7 (32%)
2	1 (4.5%)
Delayed Recall	
0	9 (41%)
1	4 (18%)
2	3 (14%)
3	4 (18%)
4	2 (9.1%)
Orientation	
3	3 (14%)
4	3 (14%)
5	7 (32%)
6	9 (41%)
Total	16 (11, 20)
n (%); Median (IQR)	

Table S3: Ocular parameters and visual function among the study participants

	N	**Cases (N=22)**	**Control (N=20)**	**Test Statistic**
Right Eye				
Best-corrected visual acuity (BCVA)	42	0.3 0.4 0.4	0.3 0.4 0.4	$F_{1,40}=0.00, P=0.97^{¥}$
Intraocular pressure (IOP)	42	13.0 14.0 14.1	13.0 14.0 14.0	$F_{1,40}=0.06, P=0.80^{¥}$
Total RNFL thickness	42	101.8 106.5 115.3	99.2 107.5 112.6	$F_{1,40}=0.32, P=0.58^{¥}$
Superonasal	42	108.0 126.5 154.0	136.5 147.0 160.7	$F_{1,40}=8.73, P=0.01^{¥}$
Inferonasal	42	128.9 137.0 140.8	102.4 114.0 131.2	$F_{1,40}=21.01, P<0.01^{¥}$
Nasal	42	74.0 89.0 97.2	66.4 83.5 90.8	$F_{1,40}=3.29, P=0.08^{¥}$
Temporal	42	66.0 78.0 84.0	73.2 77.5 85.6	$F_{1,40}=1.27, P=0.27^{¥}$
Choroidal thickness	42	187.6 219.5 268.8	258.8 288.0 310.3	$F_{1,40}=10.64, P<0.01^{¥}$
Left Eye				
Best-corrected visual acuity (BCVA)	42	0.3 0.4 0.4	0.3 0.4 0.4	$F_{1,40}=0.00, P=0.97^{¥}$
Intraocular pressure (IOP)	42	13.0 14.0 14.0	13.0 14.0 14.0	$F_{1,40}=0.07, P=0.79^{¥}$
Total RNFL thickness	42	99.7 112.5 117.3	101.1 110.5 112.0	$F_{1,40}=0.35, P=0.56^{¥}$

Superonasal	42	109.8 128.0 150.4	122.2 136.5 162.8	$F_{1,40}=3.93$, $P=0.05$¥
Inferonasal	42	123.0 131.0 152.7	113.4 128.5 131.0	$F_{1,40}=4.48$, $P=0.04$¥
Nasal	42	70.5 79.5 95.2	77.4 84.5 97.0	$F_{1,40}=2.62$, $P=0.11$¥
Temporal	42	65.8 75.0 82.3	66.0 69.0 74.6	$F_{1,40}=0.48$, $P=0.49$¥
Choroidal thickness	42	189.8 220.5 262.3	236.2 260.5 319.6	$F_{1,40}=8.91$, $P<0.01$¥
RNFL retinal nerve fiber layer, N is the number of non-missing values. ¥Wilcoxon rank-sum test.				

Table S4: Imaging Metrics in Specific Brain Regions of Patients with Parkinson's Disease

	N	Cases (N=22)	Control (N=20)	Test Statistic
Fractional anisotropy (FA)				
Rt Cingulate	34	0.4 0.4 0.4	0.8 0.9 1.0	$F_{1,32}=70.54$, $P<0.01$¥
Lt Cingulate	34	0.4 0.4 0.4	0.7 0.8 0.8	$F_{1,32}=71.66$, $P<0.01$¥
Corpus callosum, genu	34	0.7 0.7 0.7	0.8 0.9 0.9	$F_{1,32}=53.77$, $P<0.01$¥
Corpus callosum, splenium	34	0.7 0.7 0.8	0.8 0.9 1.0	$F_{1,32}=21.56$, $P<0.01$¥
Rt Substantia nigra	34	0.5 0.5 0.6	0.4 0.4 0.4	$F_{1,32}=69.21$, $P<0.01$¥
Lt Substantia nigra	32	0.5 0.6 0.6	0.4 0.4 0.4	$F_{1,30}=36.17$, $P<0.01$¥
Mean diffusivity (MD)				
Rt Cingulate	34	0.8 0.8 0.9	0.3 0.4 0.6	$F_{1,32}=70.57$, $P<0.01$¥
Lt Cingulate	34	0.8 0.8 0.9	0.4 0.5 0.6	$F_{1,32}=70.30$, $P<0.01$¥
Corpus callosum, genu	34	0.8 0.8 0.9	0.4 0.4 0.4	$F_{1,32}=30.18$, $P<0.01$¥
Corpus callosum, splenium	34	0.7 0.8 0.9	0.4 0.4 0.4	$F_{1,32}=74.45$, $P<0.01$¥
Rt Substantia nigra	34	0.8 0.9 0.9	0.8 0.8 0.8	$F_{1,32}=72.35$, $P<0.01$¥
Lt Substantia nigra	34	0.8 0.8 0.9	0.8 0.8 0.8	$F_{1,32}=20.86$, $P<0.01$¥
N is the number of non-missing values. ¥Wilcoxon rank-sum test.				

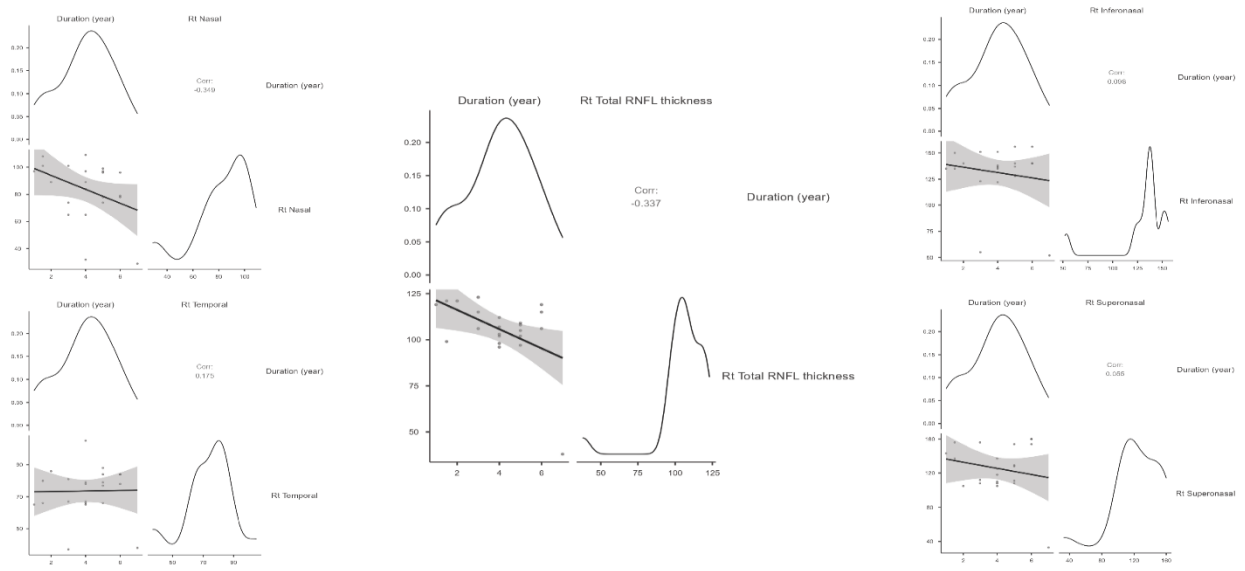

Figure S1 displays the correlation between the right retinal nerve fiber layer (RNFL) thickness and the duration of the disease.

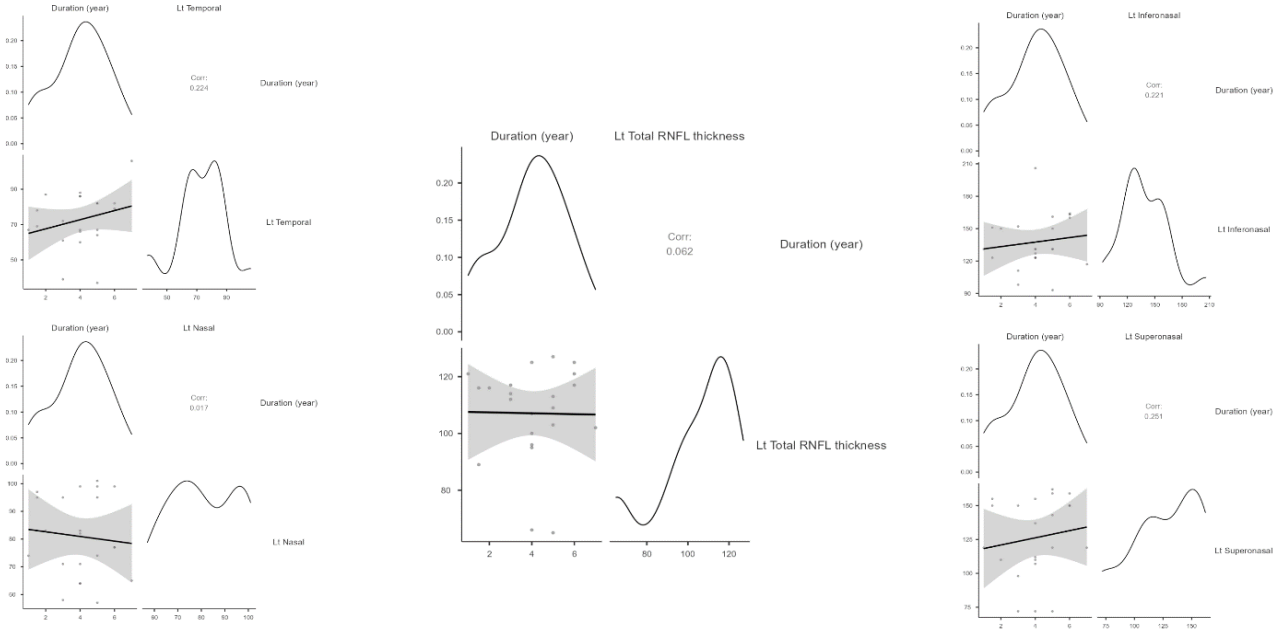

Figure S2 displays the correlation between the left retinal nerve fiber layer (RNFL) thickness and the duration of the disease.

Citation

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