Correlation Between Structural and Functional Retinal Changes in Parkinson Disease

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Background: To evaluate structural changes in the retina and correlate those with visual function measurements in patients with Parkinson disease (PD).

Methods: A cross-sectional comparative study of 20 patients with PD and 20 age-matched healthy controls was conducted. Visual acuity, color vision, contrast sensitivity, visual fields, pattern visual-evoked response (VER), and multifocal electroretinogram were recorded to determine functional change, whereas structural changes were evaluated with retinal nerve fiber layer (RNFL) thickness, macular thickness, macular volume, and ganglion cell–inner plexiform layer complex (GCL-IPL) thickness using spectral domain ocular coherence tomography (SD-OCT).

Results: PD patients ranged from Stage 1–3, with median Stage 2 (Hoehn and Yahr Classification) with mean Unified Parkinson Disease Rating Scale III score of 19 ± 10.42, and average disease duration of 5.8 ± 2.78 years. Visual acuity, color vision, and visual fields were unaffected but contrast sensitivity was significantly worse than controls ($P < 0.001$). Multifocal electroretinogram values in the central 2° field revealed decreased foveal electrical activity, with increased pattern VER amplitude and latency. Significant RNFL thinning was observed in the average RNFL ($P = 0.033$), superior ($P = 0.018$), and temporal ($P = 0.036$) quadrants. Significant ganglion cell layer loss was captured on SD-OCT with average, minimum GCL-IPL, and all 6 sectors showing thinning ($P \leq 0.003$). The functional changes correlated significantly with structural changes, disease duration, and severity. There was no correlation between structural changes in the retina and disease duration or severity.

Conclusions: Subclinical visual dysfunction was observed in patients with PD with good structural–functional correlation. GCL-IPL thinning may be a more reliable parameter than RNFL thickness for structural alterations of the retina in patients with PD.

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Parkinson disease (PD) is a progressive motor disorder associated with the degeneration of dopaminergic neurons in the basal ganglia substantia nigra pars compacta region of the mid brain, with increasing prevalence of the disease with aging. It is primarily characterized by motor manifestations, such as resting tremor, rigidity, and bradykinesia, although nonmotor involvement such as that of the visual system is also seen.

Dopamine, besides its major involvement in motor function, has also been fully established as a neurotransmitter and modulator in the retina, specifically in the inner nuclear layer and inner plexiform layers (1). These dopaminergic neurons in the retina modulate the receptive field of ganglion cells to partially control visual functions including spatial contrast sensitivity and color vision, which are often impaired in PD (1,2).

Optical coherence tomography (OCT) has been used to demonstrate structural changes in the peripapillary retinal nerve fiber layer (RNFL) in some patients in PD (3–7). Visual dysfunction has been documented in PD; multifocal electroretinogram (mfERG) testing has demonstrated decreased electrical activity at the fovea (8). However, it is as yet unclear whether the functional loss is concurrent with the structural damage in the retina.

This study evaluated the relationship between structure and function in patients with PD.

METHODS

We conducted a cross-sectional comparative study at a tertiary care center for ophthalmology and neurology,

after prior approval from the registered institutional ethics committee and in compliance with the tenets of the Declaration of Helsinki.

Patients were recruited from the neurology outpatient department who met the study criteria. Sample size was calculated to detect a difference of 10 μm in average RNFL thickness, with a power of 90% and confidence interval (CI) of 95% (9). The required sample size was 20 patients in each group.

The study group consisted of individuals with known idiopathic PD (diagnosed on the basis of United Kingdom Parkinson Disease Society Brain Bank clinical diagnostic criteria) and twenty age-matched healthy controls with no systemic or ocular disease (10). Disease duration was based on the patients' recollection of onset of symptoms. Both eyes of all patients were included in concordance with a previous recommendation in literature resulting from an observed interocular asymmetry in PD (11). Patients with coexisting neurodegenerative disorders or an ocular disease likely to demonstrate OCT changes or preclude accurate examination, and those unwilling or unable to cooperate for examination were excluded from the study. Informed consent was obtained from all study participants.

All enrolled patients underwent a detailed history, ocular and neurological examinations, and investigations to evaluate visual function. Severity of disease was assessed by Modified Hoehn and Yahr (H&Y) Scale and Unified Parkinson Disease Rating Scale III (UPDRS-III) (12,13).

Each eye was subjected to each testing modality. Best-corrected visual acuity was recorded on the Snellen chart under standard illumination. Color vision was assessed using Ishihara pseudoisochromatic test plates, and contrast sensitivity was measured by the Pelli–Robson chart. Pattern visual-evoked response (VER) was recorded using the Nicolet Ganzfeld 2015 visual stimulator and monitor (Nicolet Biomedical, Madison, WI). Monocular whole-field stimulation with a checkerboard pattern (reversal time of 500 milliseconds) was used, and all the patients were tested from a distance of 1 m. Pattern VER records the electrical activity of the visual cortex created by stimulation of the retina and is useful in measuring optic nerve function and monitor macular pathway. Pattern VER amplitude and latency were analyzed. Visual fields were recorded by the automated Visual Field Analyser 750*i* (Carl Zeiss Meditec Inc, Dublin, CA) 30-2 SITA Standard strategy, and kinetic perimetry (Haag-Streit AG, Köniz, Switzerland) was performed in patients with twice unreliable automated visual fields. Visual field results were considered reliable if the false-positive and false-negative responses were lower than 33% and fixation losses lower than 20%. Multifocal electroretinogram was recorded using Metrovision monitor system. Multifocal ERG produces topographical maps of retinal function and measures the photoreceptor integrity and post-receptoral activity. The root mean square (RMS) signal and waveform in the central 2° zone was analyzed. The RMS analysis characterizes the energy content of each response. S/Sp is the ratio between RMS value in a given zone and RMS value of periphery. The typical waveform of the basic mfERG response is a biphasic wave with an initial negative deflection followed by a positive peak. There is a second negative deflection after the positive peak. These 3 peaks are called N1, P1, and N2, respectively. N1/Np and P1/Pp signify the ratio of the amplitude of these waves in a given zone to the amplitude of these waves in periphery. P1/N1 signifies the ratio of the amplitude of the P1 wave to the amplitude of the N1 wave in a given zone.

Spectral domain optical coherence tomography (SD-OCT) was done using Cirrus HD-OCT Model 4000 (Carl Zeiss Meditec Inc, Dublin, CA) and was used to assess RNFL thickness using an Optic Disc Cube 200 × 200 scan. Average RNFL thickness was analyzed in 4 quadrants. Macular volume was assessed using a Macular Cube 512 × 128 scan, and a high-definition crosshair scan was also acquired, with each high-definition scan composed of 1024 A-scans. Ganglion cell analysis algorithm was used to analyze the ganglion cell–inner plexiform layer complex (GCL-IPL) separately. GCL-IPL was analyzed according to 6 sectors, in addition to average and minimum thickness values.

Statistical analysis was carried out using Stata 11.0 (College Station, TX). Data were presented as median (range) or mean ± SD as appropriate. The visual acuity, contrast sensitivity, multifocal ERG, pattern VER, RNFL thickness, GCL-IPL thickness, macular thickness, and volume were compared between the 2 groups using generalized estimating equation because these values were measured from both the eyes and the controls were age-matched with the cases, which made the data correlated. The correlation of structural and functional changes in retina with each other and with disease duration and severity were evaluated using Spearman rank calculation coefficient. The *P* value less than 0.05 was considered significant.

RESULTS

Twenty patients (40 eyes) with PD and 20 (40 eyes) age-matched healthy controls were examined. The mean age of individuals with PD was 58.6 ± 9.5 years (range, 37–73 years) and of controls was 58.4 ± 9.3 years (range, 37–73 years). The severity of disease was 2 (median) with a range of 1–3 (Modified Hoehn & Yohr Scale). The mean UPDRS-III score was 19 ± 10.4 (range, 7–51). The average duration of the disease was 5.8 ± 2.8 years (range, 2–10 years).

The median best-corrected visual acuity in cases was 20/20 (range, 20/20 to 20/32); and in controls, it was 20/20 (range, 20/20 to 20/32) with a *P* value of 0.481. The anterior segment, intraocular pressure, and fundus appearance were within normal limits in both cases and controls. Color vision was within normal limits in all the patients. The contrast sensitivity was significantly decreased in

patients with PD (1.46 ± 0.11) as compared with controls (1.56 ± 0.07) with a *P* value <0.001 (difference 0.19 [95% CI, 0.04–0.15]). Visual fields were found to be normal in all cases and controls. Nine patients with PD had unreliable visual fields despite twice repeating the test. In these cases, kinetic visual fields were performed and were within normal limits. One control with unreliable automated visual fields had normal kinetic visual fields.

A generalized decrease in retinal electrical activity was observed on mfERG in our patient cohort. Multifocal ERG values were analyzed in the central 2° field, representing the foveal electrical activity. RMS signal, S/Sp ratio, (ratio of RMS value in central 2° and RMS value in periphery), amplitudes (in nanovolts) of N1 and P1 waves were decreased, and P1 and N2 wave implicit times were prolonged in patients with PD. There was no difference in N1 wave implicit time (in milliseconds), N2 wave amplitude, and P1/N1 ratio between cases and controls (See **Supplemental Digital Content**, Table E1, http://links.lww.com/WNO/A147).

The pattern VER average amplitude was 9.4 ± 2.3 μV in patients with PD and 8.3 ± 1.6 μV in controls (*P* value: 0.036; difference 1.15 [95% CI, 0.1–2.2]). The pattern VER latency was also increased and was 110.2 ± 8.6 milliseconds and 105 ± 3.1 milliseconds in controls (*P* value: 0.015; difference 5.15 [95% CI, 1.0–9.3]).

Significant RNFL thinning was found in our patients in superior (*P* value: 0.018) and temporal (*P* value: 0.036) quadrants, with the average RNFL (*P* value: 0.033) also being thinner than normal age-matched controls. There was no difference in nasal and inferior quadrants between patients and controls (See **Supplemental Digital Content**, Table E2, http://links.lww.com/WNO/A148).

The GC-IPL complex was significantly thinner in cases of PD in an all 6 sectors. The average and minimum GCL-IPL values were also decreased in cases as compared with controls (*P* value ≤0.001) (See **Supplemental Digital Content**, Table E3, http://links.lww.com/WNO/A149).

There was no difference in average macular thickness (patients: 269.2 ± 17.2 μm; controls: 273.1 ± 10.9; *P* = 0.3; difference −3.9 [95% CI, −11.3 to 3.5]), central macular thickness (cases: 241.7 ± 31.8; controls: 247.1 ± 17.7; *P* = 0.2; difference −5.4 [95% CI −14.0 to 3.3]) and macular volume (cases: 9.7 ± 0.6 μm^3; controls: 9.8 ± 0.4 μm^3; *P* = 0.4; difference −0.1 [95% CI −0.3 to 0.2]).

The structural and functional changes in the retina were correlated with the disease duration and severity and were also correlated with each other. A significant correlation was observed between the functional changes in retina (pattern VER latency, RMS signal, and P1 wave amplitude) and both disease duration and severity. The structural changes on OCT (RNFL and GCL-IPL thickness) did not significantly correlate with either disease duration or severity, except for an inverse correlation between UPDRS-III score and average RNFL thickness. A weak but significant correlation was also observed between structural changes on OCT (RNFL and GCL-IPL thickness) and functional changes on mfERG (RMS signal and P1 wave amplitude). Pattern VER latency correlated significantly with RNFL thickness but not with GCL-IPL thickness (See **Supplemental Digital Content**, Table E4, http://links.lww.com/WNO/A150).

DISCUSSION

In our study, patients with PD had normal visual acuity, color vision, and visual fields, although significant contrast sensitivity abnormalities were observed. Previous reports have documented declining visual acuity with increasing disease severity, yet our results do not support this finding, possibly because of the relatively early stage of disease of recruited patients (14). Contrast sensitivity was shown to be a more sensitive parameter (15,16) of visual function, and this was the only visual functional abnormality detected.

Our patients had normal visual fields. In cases where automated fields were unreliable, a manual kinetic perimetry demonstrated normal results. Keeping in mind the conflicting reports in literature regarding visual field changes in patients with PD, it is likely that fields remain preserved at least in the mild-to-moderate stages of the disease (3,8,17).

Pattern VER amplitude and latency were increased in cases of PD. All patients with PD were on dopaminergic drugs, and this might explain the increase in pattern VER amplitude (18). Increased pattern VER latency signifies electrophysiological dysfunction in patients with PD, which has been demonstrated in earlier studies using VEP and pattern ERG (19–22). Pattern VER latency is less likely to be affected by dopaminergic drugs and seems to be a more sensitive measure of foveal electrical activity than pattern VER amplitude. Multifocal ERG in central 2° revealed reduced foveal activity in patients with PD. Only 1 previous study used mfERG in cases of PD with similar results (8). We are unaware of any reports on the effect of dopaminergic drugs on multifocal ERG in patients with PD. VEP measures the integrity of the entire visual pathway, whereas multifocal ERG is specific for local retinal function, and this may in part explain the decreased amplitude observed in mfERG despite dopaminergic treatment. The decreased foveal electrical activity and abnormal contrast sensitivity in the presence of normal visual acuity may be used to detect early subclinical visual functional impairment in PD.

RNFL thickness analysis revealed thinning in the superior, temporal, and inferior quadrants of patients with PD compared with controls. The effect of PD on structural aspects of the retina has led to reports with conflicting results (3,8,9,23). However, a recent meta-analysis has shown a generalized RNFL thinning in all quadrants (5). The RNFL represents axons of the ganglion cells and impoverished dopaminergic input to the ganglion cells, which leads to atrophy of these selected fibers, which reflects as

RNFL thinning (1,2,24). In addition, we postulate that glutamate and neurotrophin deprivation in PD can activate ganglion cell apoptosis, which may explain the GC-IPL thinning noted in our study (2,24). We used the Cirrus HD-OCT ganglion cell analysis algorithm, which can automatically segment macular GCL-IPL and measure GCL-IPL thickness with excellent intervisit reproducibility (25). Previous studies have evaluated ganglion cell layer or inner retinal layers using different segmentation algorithms with similar results (26,27).

Disease duration and severity correlated with electrophysiological changes in the retina of patients with PD. With increasing duration and severity of the disease, there was increased pattern VER latency and decreased foveal electrical activity on mfERG. Increasing severity of structural alterations on OCT, detected by RNFL and GCL-IPL thinning were related to decrease in foveal electrical activity. This suggests some degree of structural–functional correlation although the patient may have only subclinical visual dysfunction in the form of impaired contrast sensitivity. There was no clear relationship between the duration and severity of disease with structural changes on OCT. Only the UPDRS-III score was inversely correlated with RNFL thickness, possibly because our patients were in mild-to-moderate stages of disease. Earlier studies attempting to correlate disease duration and severity with retinal changes have shown variable results (4,28,29).

The small sample size and inability to include advanced stages of PD were limitations of our study. The pathological changes in PD are expected to increase with increasing severity of the disease. Our lack of patients with advanced PD (Stages 4 and 5) may have been a factor in our inability to correlate disease severity with structural alterations on SD-OCT.

In conclusion, contrast sensitivity and mfERG were found to be sensitive indicators of visual dysfunction, whereas the ganglion cell layer-inner plexiform layer analysis was a sensitive indicator of structural alterations in patients with PD. There is a subclinical visual dysfunction even in early stages of PD, which correlates with structural changes in the retina.

STATEMENT OF AUTHORSHIP

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