Inner Retinal Layer Thinning in Parkinson Disease

Mohammedyusuf E. Hajee, MD; Wayne F. March, MD; Douglas R. Lazzaro, MD; Arthur H. Wolintz, MD; Eric M. Shrier, DO; Sofya Glazman, MD; Ivan G. Bodis-Wollner, MD, DSc

Objective: To quantify retinal thickness in patients with Parkinson disease (PD).

Methods: Forty-five eyes of 24 PD patients and 31 eyes of 17 control subjects underwent a comprehensive ophthalmologic examination. We used optical coherence tomography to examine retinal thickness, separately quantifying the inner and outer retinal layers. Intraocular pressure was measured by Goldmann applanation tonometry.

Results: The mean (SD) ages of the patients with PD and healthy subjects were 64.0 (6.5) years vs 63.5 (10.7) years (P = .77). The mean (SD) intraocular pressure was 13.6 (+/- 2.7) mm Hg in the PD patients. No difference was found in either the superior or inferior outer retinal layer thickness of PD vs control eyes. The mean (SD) superior inner retinal layer thickness of PD vs control eyes was 88.79 (11.3) µm vs 103.5 (24.3) µm (P = .01), and the mean inferior inner retinal layer thickness was 89.83 (11.1) µm vs 104.0 (23.5) µm (P = .01).

Conclusions: The inner retinal layer is significantly thinner in PD patients than in healthy subjects. Idiopathic PD, distinct from glaucoma, needs to be considered in the differential diagnosis of retinal nerve fiber layer thinning.


Parkinson disease (PD) is a common neurodegenerative disease characterized by a loss of dopaminergic neurons in the basal ganglia—substantia nigra pars compacta of the midbrain; this disease affects 1% of adults older than 60 years in the United States. It was originally described in 1817 by James Parkinson as “shaking palsy.” However, it has been progressively recognized that PD also affects the autonomic, olfactory, and visual systems. Initially, the evidence of visual deficit in PD was obtained by functional measurements, such as the visual evoked potential and contrast sensitivity (CS). It was shown that the human retina contains dopaminergic amacrine cells and that retinal dopamine content and metabolites are substantially lowered in PD patients. However, direct functional evidence of retinal involvement in PD first emerged from electroretinography. Pattern electroretinographic (PERG) responses in humans with idiopathic PD were similar to those obtained in the monkey model of PD and in the monkey eye treated with intracocular 6-hydroxydopamine, a known toxin of dopaminergic neurons.

Recently, direct morphologic evidence of retinal involvement in PD emerged from time-domain optical coherence tomography (OCT). Inzelberg et al first reported significant peripapillary retinal nerve fiber layer losses in 10 patients and Altintas et al most recently confirmed this in another 17 patients. In our study, we used Fourier-domain OCT, with superior resolution and stability, compared with the earlier OCT (time-domain) method. We evaluated the inner retinal layer (IRL) and outer retinal layer (ORL) in each eye and measured intraocular pressures (IOPs) as a potential contributing variable for retinal thinning. The results show that the IRL is thin in patients with relatively early PD and the loss of nerve fiber layer in patients with PD is not secondary to increased IOP.

Methods

Study Participants

Consecutive patients who were diagnosed as having idiopathic PD, based on the accepted UK Brain Bank criteria, were enrolled in the study by neurologists with a special interest in PD. Exclusion criteria were coincident posterior-pole disease, such as macular degeneration or any optic neuropathy due to glaucoma or ischemic optic neupopa-
PD patients were undergoing pharmacologic therapies (SD) ages of the healthy subjects and PD patients were 63.5 years vs 68.9 years (P = .77). Twelve (52%) of the treated PD patients, 7 were treated with presynaptic (levodopa) medications, 4 were taking a combination of levodopa and a dopamine receptor agonist, and 1 was taking pramipexole alone. Their disease stages ranged from 2 to 3, with a mean of 2.5.

### RESULTS

In Figure 1 and Figure 2 we show the retina of a healthy individual and a patient with PD, respectively, who are roughly the same age. The paramacular area from where measurements were taken is indicated in millimeters.

### INFERIOR AND SUPERIOR IRL THICKNESSES

The mean (SD) inferior IRL thickness of healthy eyes vs PD eyes was 104.0 (23.5) µm vs 88.79 (11.1) µm (P = .01). The mean superior IRL thickness of healthy eyes vs PD eyes was 103.5 (24.3) µm vs 88.79 (11.3) µm (P = .01). Clearly, the inferior and superior IRLs are similarly affected in PD patients, and the paramacular inner retina is approximately 15% thinner than the retina of PD patients in age-matched control subjects (Table).
ORL THICKNESS

The ORL thickness was also analyzed in the same manner as the IRL. The mean (SD) superior ORL thickness of healthy eyes vs PD eyes was 170.2 (+/−23.8) µm vs 170.4 (+/−7.67) µm (P=0.88). The mean (SD) inferior ORL thickness of healthy eyes vs PD eyes was 168.2 (+/−22.9) µm vs 167.9 (+/−7.86) µm (P=0.99). A factorial analysis of variance (general linear model) was used to examine if the difference between the right and left eye was dependent on PD diagnosis using the interaction between 2 factors: laterality (right, left eye) and PD diagnosis (PD, no PD). This interaction was not significant for either the superior or inferior IRL or ORL (Table).

INTEROCULAR COMPARISON OF IRL THICKNESS IN EARLY PD

**Figure 3** illustrates a correlation between the left and right eyes of patients with relatively early PD. The corresponding statistics revealed a correlation coefficient of 0.82. **Figure 4** shows a correlation between the left and right IRL thickness of patients with relatively early PD. The corresponding statistics revealed a correlation coefficient of 0.82.

CORRELATION BETWEEN MEAN IRL AND ORL IN EARLY PD

An insignificant correlation was also found between IRL and ORL thickness in the eyes of patients with relatively early PD. The corresponding statistics revealed a correlation coefficient of 0.33.

THE EFFECT OF TREATMENT

The mean (SD) superior nerve fiber layer thickness measurements of the treated eyes and untreated eyes were 87.0 (+/−11.17) µm and 91.05 (+/−7.14) µm (P=0.25), respectively. The mean (SD) inferior IRL thickness measurements of the treated eyes and untreated eyes were 89.51 (+/−9.52) µm and 91.04 (+/−8.12) µm (P=0.67), respectively. The mean (SD) superior ORL thickness measurements of the treated eyes and untreated eyes were 171.8 (+/−5.59) µm and 168.7 (+/−9.8) µm (P=0.20), respectively. The mean (SD) inferior ORL thickness of the treated eyes and untreated eyes was 169.2 (+/−6.02) µm and 164.4 (+/−10.01) µm (P=0.45), respectively.

DISEASE DURATION AND IOP

The time elapsed from PD diagnosis compared with the severity of retinal findings was not statistically significant (P=0.11). The mean (SD) IOP was 13.6 (+/−2.7) mm Hg in PD patients. The correlation of IOP to nerve fiber layer thickness was not statistically significant (r=0.26, P=0.034).

COMMENT

Our study demonstrates a thinning of the IRL in the macular region in PD eyes. Inzelberg et al\(^\text{18}\) reported a stronger effect in the inferior peripapillary quadrant. Our results in PD suggest that the mean thickness of both superior and inferior macular hemispheres is roughly equal. However, looking at individual results, we found that 58% of the superior and 73% of the inferior IRL thickness of PD eyes fell outside 1 SD. When studying the same patients in 1.5 SDs, 47% of the superior PD IRL and 62% of inferior PD IRL fell outside the range. Clearly, a further comparison of inferior and superior IRL is needed for the paramacular region in a larger number of patients.

Recently, Altintas et al\(^\text{19}\) reported on the correlation of disease severity with inner foveal but without macular or peripapillary thickness in 17 PD eyes. We examined a 6-mm macular section, which correlates with 17° of central vision. The IRL contains both the ganglion and the amacrine cell layers and is approximately 15% to 20% thinned in this region of the PD retina. Perhaps this modest loss is the reason for the absence of disc pallor in PD despite ganglion cell damage, a result also demonstrated by Yavas et al.\(^\text{22}\) However, the 15% to 20% loss in total IRL thickness does not necessarily cause a minor loss as far as vision is concerned.
Although visual acuity is only minimally affected in patients with well-corrected PD, they lose foveal CS to patterns to which healthy observers are most sensitive (need the least contrast to detect). However, levodopa treatment improves CS.

The PERG is a measure of retinal ganglion cell activity. In both PD and the monkey model, PERG shows a specific spatial frequency deficit similar to the spatial frequency selective CS loss in PD. Spatial frequency is one standard measure of the fineness or coarseness of the visual stimulus; it consists of alternating dark and bright bands (grating pattern). In healthy observers and monkeys, when PERG response or contrast sensitivity is plotted against spatial frequency, the resulting curve is nonmonotonic: it shows a peak that represents the best visible spatial frequency pattern. This is called spatial frequency tuning. Tuning reflects the interplay of antagonistic center or surround organization of foveal ganglion cell receptive fields. Tuning is attenuated or absent in CS or PERG in PD patients. On the basis of the effects of selective D1 and D2 receptor blockers on PERG of the monkey, we modeled the preganglionic dopaminergic circuit, which modulates the balance of center and surround the organization of foveal ganglion cells of the primate. The model quantifies the way that dopaminergic amacrine cells, although sparsely distributed, control the tuning of foveal ganglion cells via separate D1- and D2-linked receptors and the way that dopaminergic amacrine cell dysfunction may result in absent spatial frequency tuning.

Retinal thinning may be relevant to the early diagnosis and neuroprotective treatment of PD. Most of our patients were in the early stages of the disease. On the basis of the distribution of Lewy bodies at different stages of PD, Braak et al suggested that PD progresses from peripheral to central neurons in a caudocranial direction. It has not been investigated whether Lewy bodies are found in the human retina of PD patients. It needs to be established whether OCT measures contribute a quantitative measure to the early diagnosis of PD other than a constellation of early signs.

The OCT results in PD are potentially relevant for the ophthalmologist. The IRL thinning has been reported in other diseases, such as primary open-angle glaucoma, multiple sclerosis, and Alzheimer disease. The IOP is raised in glaucoma, whereas in our PD patients the IOP was normal. In Alzheimer disease retinal thinning is predominant only in the superior quadrant. In summary, Fourier-domain OCT may contribute a quantitative imaging approach to the early diagnosis, treatment, and follow-up of progression of PD.

Submitted for Publication: May 13, 2008; final revision received January 6, 2009; accepted January 15, 2009.

Correspondence: Ivan G. Bodis-Wollner, MD, DSc, Department of Ophthalmology and Department of Neurology, Parkinson’s Disease and Related Disorders Center of Excellence, State University of New York—Downstate, 450 Clarkson Ave, Brooklyn, NY 11203 (ivan.bodis-wollner@downstate.edu).

Financial Disclosure: None reported.

Funding/Support: This study was funded by the National Parkinson Foundation. Dr Hajee was supported by an Empire Clinical Research Investigator Program–New York State Research Fellowship/Mentor Grant.

Additional Contributions: Hans Von Gizecki, PhD, provided statistical consultation. Zoya Belakovskaya, BS, and Mr. Alexander Belakovski provided technical support. Nancy Blace, MD, PhD, performed preliminary data collection. Muhammad Javaid, MD, assisted with graph preparations. Manuela E. Minko, MD, assisted in scheduling patients. Patricia Kavanagh, MD, referred and recruited patients. Hossam Attia, MD, performed a preliminary study comparing GDx Nerve Fiber Analyzer measures in patients with glaucoma and PD; he and Preeti Poley, MD, performed preliminary Glaucoma Diagnosis data collection.

In 1795, Dr Isaac Thompson concocted an eye water of zinc sulfate, saffron, camphor, and rose water. It was sold as late as 1939. This is 1 of a series of 32 medical trade cards advertising the product from 1875 through 1895.

Courtesy of: Daniel M. Albert, MD, MS.