Inner Retinal Layer Thinning in Parkinson Disease

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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.

Arch Ophthalmol. 2009;127(6):737-741

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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.[1] It was originally described in 1817 by James Parkinson as "shaking palsy."[2] However, it has been progressively recognized that PD also affects the autonomic, olfactory, and visual systems.[3,4] Initially, the evidence of visual deficit in PD was obtained by functional measurements, such as the visual evoked potential[5] and contrast sensitivity (CS).[6] It was shown that the human retina contains dopaminergic amacrine cells[7] and that retinal dopamine content and metabolites are substantially lowered in PD patients.[8,9] However, direct functional evidence of retinal involvement in PD first emerged from electroretinography.[10,11] Pattern electroretinographic (PERG) responses in humans[12] with idiopathic PD were similar to those obtained in the monkey model of PD[13] and in the monkey eye treated with intraocular 6-hydroxydopamine,[14] a known toxin of dopaminergic neurons.

Recently, direct morphologic evidence of retinal involvement in PD emerged from time-domain optical coherence tomography (OCT).[15-17] Inzelberg et al[18] first reported significant peripapillary retinal nerve fiber layer losses in 10 patients and Altintas et al[19] 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,[20] 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 neuropa-
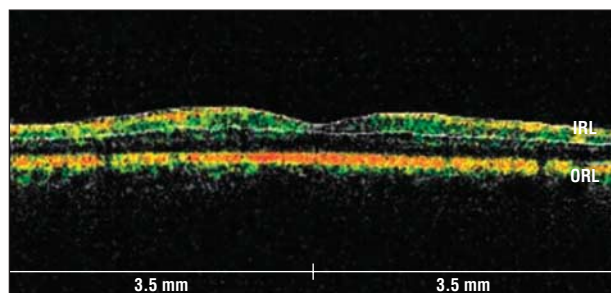
Figure 1. The retina of a healthy individual. IRL indicates inner retinal layer; ORL, outer retinal layer.
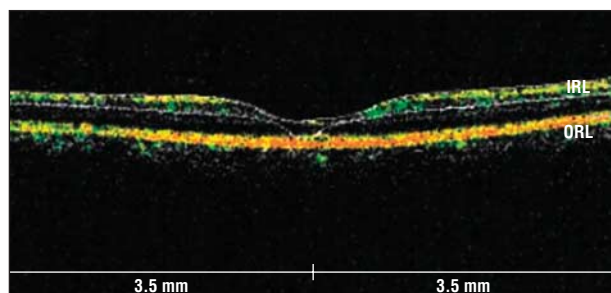

Figure 2. The retina of a patient with Parkinson disease. IRL indicates inner retinal layer; ORL, outer retinal layer.

Table. The Retinal Thickness of Healthy Individuals vs Those of PD Patients[a]

	Retinal Thickness, μm		
Retinal Area	Healthy Individuals	PD Patients	P Value
Superior IRL	103.5 (24.3)	88.79 (11.3)	.01
Inferior IRL	104 (23.5)	89.83 (11.1)	.01
Superior ORL	170.2 (23.8)	170.4 (7.67)	.88
Inferior ORL	168.2 (22.9)	167.9 (7.86)	.99

Abbreviations: IRL, inner retinal layer; ORL, outer retinal layer; PD, Parkinson disease.
[a] Data are presented as mean (SD).

thy. The erythrocyte sedimentation rate, a potentially relevant laboratory value, was normal in all study participants. The presumptive diagnosis of glaucoma was based on a history of the use of glaucoma medications, increased cupping of the optic nerve, elevated IOP (>21 mm Hg), and/or glaucomatous visual field defects. All study participants had a best-corrected visual acuity of 20/30 or better. Thirteen patients had Humphrey 30-2 visual field tested. The area of the retina evaluated by our OCT corresponds to the central/paracentral area of the visual field. None of the patients showed central/paracentral scotoma on routine visual field testing. Nine patients had their baseline ophthalmologic examination performed by ophthalmologists who provided their routine care, whereas the other patients underwent a comprehensive ophthalmologic examination by one of the coinvestigator ophthalmologists (W.F.M.) involved in this study. We studied 46 consecutive eyes of 23 PD patients. All PD patients enrolled were relatively early in their disease course, with an average duration of 2.9 years. The mean (SD) ages of the healthy subjects and PD patients were 63.5 (10.7) years and 64.0 (6.52) years (*P*=.77). Twelve (52%) of the PD patients were undergoing pharmacologic therapies

that had stabilized their disease, whereas 11 had not yet been treated with dopaminergic agents (de novo patients). 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[21] ranged from 2 to 3, with a mean of 2.5.

EQUIPMENT AND MEASUREMENTS

We used Fourier-domain OCT (RTvue; Optovue, Inc; Fremont, California) with an imaging speed of approximately 25 000 axial scans per second, which is approximately 50 times faster than time-domain detection.[17] One of the many advantages of this high speed is that it can allow the transformation from 2-dimensional to 3-dimensional imaging. The overall image quality of Fourier-domain OCT is also superior because of the elimination of many motion artifacts from the increased speed of acquisition. This is particularly relevant in PD patients with tremor. The axial resolution of a time-domain OCT is 8 to 10 μm, whereas for Fourier-domain OCT it is approximately 5 μm, which results in a more accurate representation of retinal topography.

Because a PD OCT protocol does not exist, the standard glaucoma protocol, which includes Nerve Head Map (NHM4) and Macula Map (MM7) scans (Optovue, Inc), was performed for all PD patients. The IRL includes the nerve fiber layer, the ganglion cell layer, and the inner-plexiform layer, whereas the ORL includes the layers starting from the inner nuclear layer up to and including the retinal pigment epithelium. The retinal layer measurements were 6 × 6-mm sections of the macula. Scans with artifacts such as motion and media were eliminated. Eyes of healthy (control) subjects were examined in the same way.

STATISTICAL ANALYSIS

Statistical analysis was performed using descriptive statistics and analyses of variance. To assess the reproducibility of data obtained with our instrument, we compared 2 consecutive OCT measurements in 7 healthy controls (13 eyes) in 1-week intervals. The mean IRL change was 1.25 μm. These data compare favorably with the stability data of Optovue, which claim an average variation of only 5 μm. The variability obtained with our equipment is comparable with results obtained with other equipment, such as Heidelberg retinal tomography devices.[22]

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 89.83 (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**).
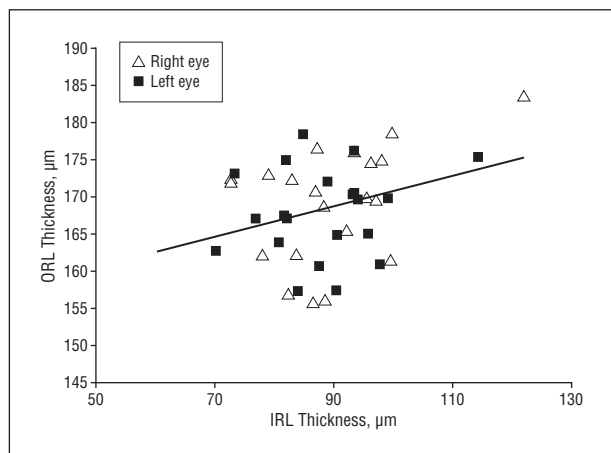
Figure 3. Correlation between the inner retinal layer thickness of the left and right eyes of patients with relatively early Parkinson disease (*r*=0.31). IRL indicates inner retinal layer; ORL, outer retinal layer.
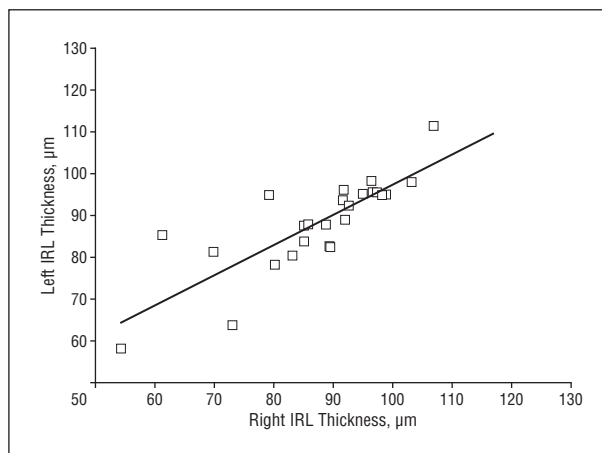

Figure 4. Correlation between the inner retinal layer (IRL) thickness of the left and right eyes of patients with relatively early Parkinson disease (*r*=0.82).

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*=.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*=.034).

COMMENT

Our study demonstrates a thinning of the IRL in the macular region in PD eyes. Inzelberg et al[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[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.[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).[6,23] However, levodopa treatment improves CS.[24]

The PERG is a measure of retinal ganglion cell activity.[25,26] In both PD and the monkey model, PERG shows a specific spatial frequency deficit[12,13] 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.[27] Tuning is attenuated or absent in CS or PERG in PD patients. On the basis of the effects of selective D_1 and D_2 receptor blockers on PERG of the monkey, we[28,29] modeled the preganglionic dopaminergic circuit, which modulates the balance of center and surrounds 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 D_1- and D_2-linked receptors and the way that dopaminergic amacrine cell dysfunction may result in absent spatial frequency tuning.[29]

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[30] 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.[31]

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,[32] multiple sclerosis,[33,34] and Alzheimer disease.[35,36] 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.[35,36] In summary, Fourier-domain OCT may contribute a quantitative imaging approach to the early diagnosis, treatment, and follow-up of progression of PD.

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Ophthalmological Ephemera

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.

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Correction

Errors in Figure and Text. In the Clinical Sciences article titled "Inner Retinal Layer Thinning in Parkinson Disease" by Hajee et al, published in the June issue of the *Archives* (2009;127[6]:737-741), errors occurred in the legend to Figure 3 and the text. The legend should have read, "Correlation between the mean inner retinal layer (IRL) and outer retinal layer (ORL) thickness in early Parkinson disease (r=0.31)." Also, in the "Results" section of the text on page 739, the paragraph entitled "Interocular Comparison of IRL Thickness in Early PD" should have immediately preceded Figure 3 and its legend and should have read, in its entirety, as follows: "**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." The paragraph entitled "Correlation Between Mean IRL and ORL in Early PD" should have read as follows: "In **Figure 4**, an insignificant correlation was found between IRL and ORL thickness in the eyes of patients with relatively early PD. The corresponding statistics revealed a correlation coefficient of 0.31."