Evaluation of Progressive Visual Dysfunction and Retinal Degeneration in Patients With Parkinson's Disease

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Purpose. To quantify changes in visual function parameters and in the retinal nerve fiber layer and macular thickness over a 5-year period in patients with Parkinson's disease (PD).

Methods. Thirty patients with PD and 30 healthy subjects underwent a complete ophthalmic evaluation, including assessment of visual acuity, contrast sensitivity vision, color vision, and retinal evaluation with spectral-domain optical coherence tomography (SD-OCT). All subjects were reevaluated after 5 years to quantify changes in visual function parameters, the retinal nerve fiber layer, and macular thickness. Association between progressive ophthalmologic changes and disease progression was analyzed.

Results. Changes were detected in visual function parameters and retinal nerve fiber layer thickness in patients compared with controls. Greater changes were found during the follow-up in the PD group than healthy subjects in visual acuity, contrast sensitivity, Lanthony color test ($P < 0.016$), in superotemporal and temporal retinal nerve fiber layer sectors ($P < 0.001$), and in macular thickness (all sectors except inner superior and inner inferior sectors, $P < 0.001$). Progressive changes in the retinal nerve fiber layer were associated with disease progression ($r = 0.389$, $P = 0.028$).

Conclusions. Progressive visual dysfunction, macular thinning, and axonal loss can be detected in PD. Analysis of the macular thickness and the retinal nerve fiber layer by SD-OCT can be useful for evaluating Parkinson's disease progression.

Keywords: Parkinson's disease, optical coherence tomography, retinal nerve fiber layer, progression, visual dysfunction

Parkinson's disease (PD) is a neurodegenerative disorder that leads to a selective loss of dopaminergic neurons, mainly in the basal ganglia of the brain. Besides the well-known movement alterations (i.e., bradykinesia, resting tremor, or rigidity) PD includes nonmotor symptoms such as dementia, depression, and autonomic dysfunction.[1] Vision is one of the nonmotor systems altered in PD, especially the visual field corresponding to the fovea.[2]

Visual alterations in PD are suggested to be caused by dysfunction of the intraretinal dopaminergic circuitry and final retinal output to the brain.[2] Patients with PD usually present decreased low contrast visual acuity (LCVA), altered contrast sensitivity vision (CSV), and subtle color deficiencies[3] as well as retinal structural affectation.[4–6] Recent studies[7–9] have demonstrated retinal thinning in PD patients compared with healthy subjects.

Retinal thinning and axonal loss have also been observed in other neurodegenerative processes such as Alzheimer's disease[10] or multiple sclerosis.[11] Progressive neurodegeneration occurs in patients with multiple sclerosis and is detectable with digital imaging devices in ophthalmology (such as spectral-domain optical coherence tomography [SD OCT]). Axonal loss in these patients can be detected after 2 to 3 years since baseline evaluation of the retinal nerve fiber layer (RNFL) by using SD-OCT.[12,13]

Despite increasing research on retinal alterations in PD, literature on progressive retinal changes in these patients is scarce. In the present study we evaluated progressive visual dysfunction and axonal degeneration by quantifying changes in visual function tests and retinal thickness in patients with PD over a period of 5 years.

Methods

Patients with confirmed idiopathic PD diagnosis were included in this prospective longitudinal study with a follow-up of 5 years. A total of 60 eyes from 30 patients, and 60 eyes from 30 healthy individuals, age and sex matched, were evaluated at baseline and at 5 years and included in the final statistical analysis. All procedures adhered to the tenets of the Declaration of Helsinki, the experimental protocol was approved by the Ethics Committee of the Miguel Servet Hospital, and all participants were provided written informed consent to participate in the study.

The diagnosis of PD was based on the United Kingdom Brain Bank Criteria[14] and information about disease severity (using

the Hoehn-Yahr [HY]),[15] disease duration, and treatment was recorded. Treatment was divided into three different categories for clearer classification: drugs that enhance dopamine levels (carbidopa, levodopa, and rasagiline), dopaminergic drugs (pramipexole, ropirinol, rotigotine), and "other" (amitriptiline, propranolol, clonazepam). Patients with significant refractive errors (>5 diopters [D] of spherical equivalent refraction or 3 D of astigmatism), intraocular pressure (IOP) $\geq$ 21 mm Hg, media opacifications, concomitant ocular diseases (including history of glaucoma or retinal pathology), and systemic conditions and/or systemic medication (such as chloroquine, tuberculostatics, and anticonvulsants) that could affect the visual system were excluded from the study. The healthy controls had no history and no evidence of ocular or neurologic disease of any nature; their best-corrected visual acuity (BCVA) was >20/30 on the Snellen scale.

Visual function was assessed by evaluating BCVA using an ETDRS chart, CSV using the Pelli-Robson and CVS-1000E tests, and color vision using the Farnsworth desaturated D15 and Lanthony desaturated D15 tests. Structural analysis of the retina was performed by using SD-OCT with Spectralis OCT (Heidelberg Technology, Heidelberg, Germany), which included two different protocols: fast macular protocol (retina application) and RNFL protocol (glaucoma application).

LogMAR BCVA was evaluated at three different contrast levels: 100% (high contrast VA [HCVA], using ETDRS chart), 2.50%, and 1.25% (LCVA, using low-contrast ETDRS chart). All measurements were obtained under monocular vision and controlled lighting conditions with best correction.

Contrast sensitivity provides more complete information about visual function than visual acuity tests. Contrast sensitivity vision was evaluated in our patients by using the Pelli-Robson chart and the CVS-1000E test. The Pelli-Robson chart comprises horizontal lines of capital letters organized into triplets, with two triplets per line. The contrast decreases from one triplet to the next, even within each line. All patients were evaluated under monocular vision at a distance of 1 m from the chart and under controlled photopic conditions (85 cd/m^2). The score corresponding to the last triplet of letters seen by the patient was recorded. The CSV-1000E instrument comprises four rows with 17 circular patches each. The patches present a grating that decreases in contrast moving from left to right across the row. Each contrast value for each spatial frequency was transformed into a logarithmic scale according to standardized values, and the resulting score was recorded. All patients were evaluated with the CSV-1000E test at a distance of 2.5 m from the chart under monocular vision at four different spatial frequencies (3, 6, 12, and 18 cycles per degree [cpd]).

Color vision was assessed with the Color Vision Recorder program, which analyzes chromatic discrimination by arrangement of colors. All patients in our study were evaluated by using the Farnsworth D15 and Lanthony D15 protocols, and different output parameters, such as the confusion index (C-index) (which represents the ratio between the patient's major radius—largest difference between caps—and the major radius of a perfect arrangement for the subject's age group), the confusion angle (Conf angle, which represents the axis of color deficiency), and the scatter index (S-index, which represents the parallelism of confusion vectors to the personal confusion angle), were recorded.[16,17] The tests were performed under monocular vision.

Structural measurements of the retina were obtained by using the Spectralis OCT device by the same experienced operator, and poor-quality scans before data analysis were rejected. The fast macular protocol of the Spectralis OCT device (retina application) uses an internal fixation source and centers on the patient's fovea. The retinal thickness map analysis protocol represents the nine subfields as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS),[18] which include a central 1-mm circle representing the fovea, and inner and outer rings measuring 3 and 6 mm in diameter, respectively. The inner and outer rings are divided into four quadrants each: superior, nasal, inferior, and temporal. Central foveal thickness was also calculated. The RNFL protocol displays in each series of scans the average RNFL thickness and six sectors of the RNFL thickness (nasal, temporal, superotemporal, inferotemporal, superonasal, and inferonasal). Retinal nerve fiber layer and retinal acquisitions were obtained by using TruTrack eye-tracking technology (Heidelberg Engineering, Heidelberg, Germany) that recognizes, locks onto, and follows the patient's retina during scanning.

All variables were registered in a database created with a commercial database application program (FileMaker Pro 8.5; File-Maker, Inc., Santa Clara, CA, USA). All subjects were evaluated after 5 years from baseline, and a longitudinal analysis was performed. Modifier variables were age, sex, and IOP. Statistical analysis was performed by using commercial predictive analytics software (SPSS, version 20.0; SPSS, Inc., Chicago, IL, USA). The normality of the sample distribution was confirmed by using the Kolmogorov–Smirnov test. Bonferroni correction for multiple comparisons was applied. Changes in visual function parameters and in the RNFL and macular thicknesses were calculated and compared between baseline and the 5-year visit by using paired Student's *t*-test, and the changes registered during the follow-up in both groups (PD patients and healthy controls) were compared by means of Student's *t*-test.

Possible associations between structural and functional changes were analyzed by means of Pearson's correlation test. A logistic regression analysis was performed to assess whether changes in any ophthalmologic parameter were predictive of change in the course of the disease (as measured with HY scale).

Results

Forty patients with PD and 40 healthy controls were completely evaluated at baseline. All patients belonged to a larger cohort group of 100 patients with PD, of whom 40 individuals completed visual function tests at baseline during the year 2011. Part of this large cohort group (including 11 patients from the present study) was also evaluated (structural and functional measurements) in 2014 and the results have been published elsewhere.[3] Ten patients were unable to follow up owing to severe physical impairment (n = 7) and the impossibility to come to our clinic for ophthalmologic evaluation (n = 3). No ophthalmic or systemic conditions matching the study's exclusion criteria were reported or observed in our patients during the study follow-up. Only five controls were unable to follow up owing to occurrence of macular disease (n = 2), important media opacifications (n = 1), and other personal reasons (n = 2). Finally, only 30 patients were able to complete the 5-year follow-up satisfactorily, thus only 30 controls were included for the final analysis. Sixty eyes from 30 patients with a mean age of 69.54 years (SD = 6.60), and 60 eyes from 30 healthy individuals with a mean age of 68.34 years (SD = 8.45) were included in the final statistical analysis. The male to female ratio was 3:2 (17 males, 13 females) for both groups. Age, sex, and IOP did not differ significantly between the groups (P = 0.177, 0.895, and 0.780, respectively). Disease duration in the group of patients at the beginning of the study was 13.56 years (SD = 6.22). The median Hoehn-Yahr stage at the beginning of the study was 2.68 (SD = 0.69) and 2.85 (SD = 0.68) when patients were

Table 1. Demographic Data of Patients With Parkinson's Disease and Controls

Demographic Parameters	Baseline	5 Year
Age in PD patients, y (SD)	69.54 (6.60)	74.61 (6.55)
Age in controls, y (SD)	68.34 (8.45)	73.40 (8.09)
Male/female in PD patients	17/13	17/13
Male/female in controls	17/13	17/13
Hoehn-Yahr score (SD)	2.68 (0.69)	2.85 (0.68)
Duration of disease, y (SD)	13.53 (6.22)	18.44 (6.19)

Data obtained at baseline and at 5-year follow-up. Abbreviation: SD, standard deviation.

evaluated 5 years from baseline ($P < 0.001$) (Table 1). "Drugs that enhance dopamine levels" was the most prescribed category at the beginning of the study (88% of patients) and combination therapy with levodopa and carbidopa was the most frequent treatment (45%). Sixty-four percent of treatments were categorized as "dopaminergic," most of which were used in combination with drugs included in the previous category. A small percentage of patients (9%) were prescribed drugs with no dopaminergic effects. These numbers remained stable during the study follow-up, although individualized drug dosage was adjusted (usually increased) in 30% of our patients during the 5-year period.

Parkinson's Disease Patients Present Progressive Visual Dysfunction

On the basis of previous cross-sectional studies where visual dysfunction in PD patients was detected, LCVA, contrast sensitivity vision, and color vision were evaluated in our patients at baseline and after 5 years to assess progressive dysfunction.

Best-corrected visual acuity (at 100% and 2.50% contrast) and CSV (at 3, 6, and 18 cpd) were significantly lower in PD subjects. Lanthony C-index presented a significant tendency toward protanomaly in PD patients compared with healthy individuals. These differences between both groups remained significant during the 5-year follow-up. Greater VA and CSV loss was observed in the PD group after 5 years from baseline than in controls. Color vision presented a greater change toward protanomaly in the patient's group as observed by Lanthony C-index and S-index, although the latter was not significant after Bonferroni correction for multiple comparisons. Results can be seen in Table 2.

Patients with PD presented worse visual outcomes than controls and significant progression of visual dysfunction during the study follow-up.

Parkinson's Disease Patients Present Progressive Retinal Thinning as Compared With Healthy Individuals

Previous cross-sectional research demonstrated significant retinal thinning in PD patients. From published studies, we evaluated macular and RNFL thickness by using OCT technology at baseline and after 5 years to assess progressive retinal thinning in these patients.

After cross-sectional comparison, no significant differences were observed in macular thickness measurements between PD patients and controls (nor at baseline nor at 5-year follow-up). However, greater macular thinning was observed in PD patients after 5 years than in healthy subjects, affecting all macular sectors (except inner superior and inner inferior sectors) ($P < 0.001$). Results can be seen in Table 3.

Patients with PD presented significant RNFL thinning affecting the superotemporal and inferotemporal sectors, compared with controls, at baseline. At 5 years these differences remained significant and were also observed in the temporal sector. A greater RNFL loss was observed in the temporal and superotemporal sectors in PD patients after 5 years of follow-up, when compared with healthy controls ($P < 0.001$). Results can be observed in Table 3; a case image can be observed in the Figure.

Patients with PD presented progressive macular and RNFL thinning, compared with healthy controls.

Progressive Structural Changes Correlate Moderately With Visual Dysfunction and Disease Progression in PD

Moderate to strong association between structural and functional changes has been previously reported in PD. We evaluated the correlation between observed progressive retinal

Table 2. Visual Function Parameters in Parkinson's Disease Patients

Functional Parameters (SD)	Basal Visit			5-Year Visit			Change in 5 Years (5-Year Visit – Basal Visit)		
	Controls	PD	*P*	Controls	PD	*P*	Controls	PD	*P*
VA 100%	0.01 (0.14)	0.09 (0.14)	**0.001**	0.01 (0.14)	0.11 (0.16)	**0.001**	0.00	0.02	**0.013**
VA 2.50%	0.42 (0.23)	0.56 (0.21)	**<0.001**	0.44 (0.20)	0.56 (0.21)	**0.007**	0.02	0.00	0.660
VA 1.25%	0.54 (0.23)	0.63 (2.25)	0.031	0.55 (0.23)	0.61 (0.23)	0.241	0.01	−0.02	**0.003**
Farnsworth C-Index	1.25 (0.40)	1.27 (0.50)	0.176	1.24 (0.35)	1.33 (0.52)	0.126	−0.01	0.05	0.781
Farnsworth S-Index	1.69 (0.46)	1.71 (0.47)	0.567	1.69 (0.44)	1.77 (0.43)	0.496	0.00	0.06	0.134
Farnsworth Conf angle	56.78 (33.33)	57.57 (33.88)	0.712	56.47 (33.07)	59.13 (15.15)	0.704	−0.31	1.56	0.238
Lanthony C-Index	1.60 (0.58)	1.71 (0.58)	**<0.001**	1.59 (0.55)	2.15 (0.46)	**<0.001**	−0.01	0.44	**0.016**
Lanthony S-Index	1.84 (0.47)	2.03 (0.49)	0.406	1.80 (0.49)	1.91 (0.41)	0.394	−0.04	−0.12	0.045
Lanthony Conf angle	55.78 (32.55)	57.96 (46.33)	0.255	59.10 (29.69)	67.11 (15.80)	0.224	3.32	9.15	0.056
Pelli-Robson	1.73 (0.18)	1.72 (0.16)	0.541	1.61 (0.21)	1.58 (0.21)	0.592	−0.12	−0.42	**<0.001**
CSV1000 3 cpd	1.53 (0.22)	1.48 (0.38)	**0.013**	1.51 (0.19)	1.40 (0.20)	**0.016**	−0.02	−0.08	**<0.001**
CSV1000 6 cpd	1.77 (0.26)	1.64 (0.31)	**0.003**	1.76 (0.20)	1.62 (0.19)	**0.004**	−0.01	−0.02	**0.016**
CSV1000 12 cpd	1.37 (0.31)	1.31 (0.35)	0.029	1.38 (0.26)	1.22 (0.34)	0.037	0.01	−0.09	**<0.001**
CSV1000 18 cpd	0.97 (0.27)	0.65 (0.41)	**0.004**	0.95 (0.26)	0.66 (0.28)	**0.005**	−0.02	0.01	0.657

Data obtained at baseline and at 5-year reevaluation. Bold values indicate statistical significance (Bonferroni correction for multiple comparisons, $P \leq 0.016$).

Table 3. Retinal Parameters in Parkinson's Disease Patients

Structural Parameters	Basal Visit			5-Year Visit			Change in 5 Years (5-Year Visit – Basal Visit)		
	Controls	PD	*P*	Controls	PD	*P*	Controls	PD	*P*
Macular thickness									
Central	278.31 (24.55)	277.49 (25.81)	0.870	276.68 (23.21)	273.02 (46.09)	0.622	−1.63	−4.47	**<0.001**
Inner superior	341.00 (15.71)	334.75 (17.03)	0.061	342.45 (27.69)	334.83 (19.84)	0.110	1.45	0.08	0.230
Inner nasal	343.80 (18.62)	338.81 (17.50)	0.171	342.41 (18.75)	329.21 (58.15)	0.135	−1.39	−9.6	**<0.001**
Inner inferior	338.96 (17.79)	331.95 (17.92)	0.053	336.47 (18.45)	332.12 (20.70)	0.268	−2.49	0.17	0.156
Inner temporal	330.17 (18.60)	324.06 (15.79)	0.080	328.58 (18.73)	315.60 (52.18)	0.106	−1.59	−8.46	**<0.001**
Outer superior	293.92 (14.14)	289.42 (13.83)	0.112	293.02 (15.12)	284.37 (31.11)	0.082	−0.9	−5.05	**<0.001**
Outer nasal	312.33 (17.29)	306.67 (14.34)	0.079	308.12 (19.27)	299.05 (36.77)	0.127	−4.21	−7.62	**<0.001**
Outer inferior	284.50 (16.85)	282.04 (16.82)	0.465	284.39 (15.13)	274.08 (38.89)	0.397	−0.11	−7.96	**<0.001**
Outer temporal	281.65 (15.14)	275.89 (12.21)	0.041	278.70 (15.19)	268.32 (38.94)	0.089	−2.95	−7.57	**<0.001**
RNFL thickness									
Average	98.19 (9.10)	96.39 (9.52)	0.344	96.81 (9.00)	93.87 (9.33)	0.023	−1.38	−2.52	0.087
Nasal	77.90 (18.61)	78.02 (14.42)	0.971	74.60 (17.18)	73.46 (15.40)	0.727	−3.3	−4.56	0.102
Temporal	71.47 (15.70)	68.51 (11.99)	0.021	69.77 (16.13)	64.79 (14.52)	**0.007**	−1.7	−3.72	**<0.001**
Superotemporal	130.02 (16.22)	126.97 (17.89)	**0.006**	129.55 (15.88)	122.04 (19.32)	**0.003**	−0.47	−4.93	**<0.001**
Inferotemporal	142.46 (16.38)	134.58 (18.10)	**<0.001**	136.46 (18.65)	129.44 (17.92)	**<0.001**	−6.00	−5.14	0.453
Superonasal	103.73 (18.24)	102.88 (19.51)	0.144	102.85 (16.13)	100.66 (19.71)	0.646	−0.88	−2.22	0.218
Inferonasal	116.10 (28.03)	114.91 (19.66)	0.221	110.44 (27.00)	108.98 (21.01)	0.097	−5.66	−5.93	0.767

Data obtained at baseline and at 5-year reevaluation, measured with spectral-domain optical coherence tomography. Bold values indicate statistical significance (Bonferroni corrections for multiple comparisons, $P \leq 0.005$ for macular measurements, $P \leq 0.007$ for RNFL thickness).

changes and visual function parameters in these patients, as well as disease progression measured with HY scale.

An inverse moderate correlation was found between the superotemporal sector of the RNFL thickness and LCVA 2.50% and 1.25% ($r = -0.405$, $P = 0.045$; $r = -0.377$, $P = 0.038$, respectively), and between the inferotemporal sector of the RNFL and VA 1.25% ($r = -0.403$, $P = 0.028$).

A moderate association between progressive RNFL thinning (superotemporal sector) and disease progression measured with the HY scale was observed ($r = -0.389$, $P = 0.028$) in patients with PD. Logistic regression analysis did not reveal any ophthalmologic parameter significantly predictive of change in the HY scale.

Based on these results, progressive structural changes correlate with visual dysfunction and disease progression in PD.

Discussion

In the present study we quantified the progressive changes in visual function parameters and in the RNFL and macular thickness in patients with PD over a follow-up time of 5 years. To the best of our knowledge, this is the first longitudinal study assessing progressive changes in the functional and retinal parameters of patients suffering from PD. Our patients presented lower contrast sensitivity scores than healthy controls as measured by means of HCVA and LCVA and lower CSV. Additionally, a protanomaly was observed in our patients, based on Lanthony's C-index, and was more evident after the 5-year follow-up. Both Farnsworth and Lanthony D15 color tests provide information for differentiating subjects with severe color vision loss from those with milder color defects or normal color vision. However, Lanthony test is less saturated than the Farnsworth color test, thus it is designed to detect more subtle color deficiencies. In our study, only Lanthony's C-index was significantly altered in PD patients after Bonferroni corrections for multiple comparisons. After 5 years, our patients presented progressive HCVA and LCVA, CSV loss, and a progressive color vision deficiency when compared with healthy controls. Visual dysfunction has previously been reported in PD patients as well as abnormalities in neurophysiological tests.[19] These alterations have been linked to dopamine depletion in the retina of PD patients,[19] which explains progression of visual dysfunction as observed in our patients.

Our patients also presented greater progressive macular thinning and RNFL loss than controls. Alteration of the retinal layers in PD was first demonstrated in 2004 by Inzelberg et al.[20] Since then, several studies[5,8,9,20–23] have demonstrated different results. Retinal nerve fiber layer thinning has been observed by Inzelberg et al.[20] and Altintas et al.[21] However, more recent research has not found significant changes in the RNFL thickness of PD patients,[22,23] despite a large sample size.[22] Cross-sectional analysis of macular measurements in PD patients also has shown contradictory results: macular volume is significantly reduced in PD as reported by Altintas et al.[21] and Chorostecki et al.[23]; however, Bittersohl et al.[22] have not found significant differences in macular volume between patients and controls. Sample sizes included in these studies differ greatly, and different OCT devices (Stratus OCT [Carl Zeiss Meditec, Inc., Dublin, CA, USA] versus Heidelberg OCT) were used and may account for disparate results. Previous studies[4,5,9] performed by our team have confirmed that macular thickness and the RNFL are affected in PD, especially in the inferior and temporal quadrants. Results in this current study showed significant differences in superotemporal and inferotemporal sectors of the peripapillary RNFL, which support our previous findings. Interestingly, progressive changes in the RNFL were also associated with functional changes and disease progression as measured with the HY scale. Previous cross-sectional studies[4,22] have demonstrated an inverse correlation between HY scores and macular measurements.

Although PD patients had lower macular thickness, statistical differences between both groups were not found either at baseline or at the 5-year follow-up, contrary to our previous results.[5,9] Differences in the sample size (our previous research was based on a larger number of subjects) may account for these discrepancies. However, even though no

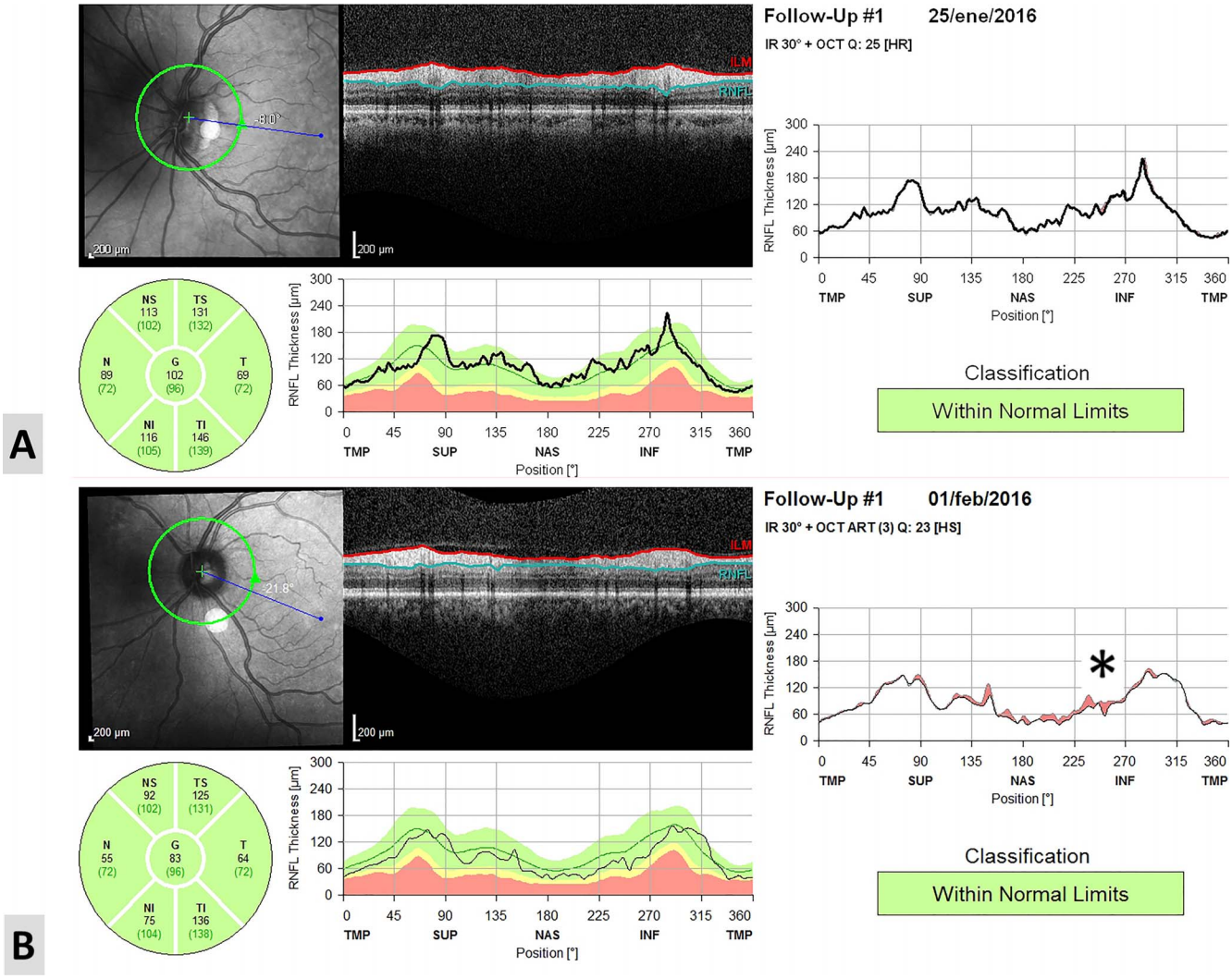

FIGURE. Retinal nerve fiber layer analysis by OCT in a patient with PD and a healthy control. (**A**) Healthy control. (**B**) Parkinson's disease patient. The OCT report compares current analysis with the baseline evaluation (5 years prior). The graphic on the *right side* of each report shows marked changes (thinning) in the RNFL. Compared to the healthy control, the patient shows progressive RNFL loss in the superior, nasal, and inferior sectors of the optic nerve, marked with an asterisk (*).

cross-sectional differences were found, significant progressive changes in the macular area were found between the two groups during the 5-year follow-up, with greater macular thinning affecting the retina of PD subjects. Prior research on another neurodegenerative process, multiple sclerosis (a neurodegenerative disease widely studied for the past decade), has demonstrated progressive RNFL loss in multiple sclerosis patients at 2 and 3 years' follow-up.[12,13] However, few of these studies have analyzed progressive macular changes. Garcia-Martin et al.[12] have found progressive macular changes in multiple sclerosis affecting macular average thickness. Macular volume, on the other hand, is not progressively affected in these patients.[12,13] With the introduction of the segmentation analysis of the retinal layers in the past 5 years, further information about progressive retinal thinning has been obtained in neurodegenerative processes, suggesting progressive loss of macular ganglion cells in multiple sclerosis.[24] Ganglion cell loss has also been detected in PD patients in previous cross-sectional studies using segmentation analysis of the retinal layers.[6,23] However, we could not find any previous published longitudinal studies on progressive macular and RNFL changes in PD to corroborate our findings.

Our results also showed an inverse correlation between progressive thinning of the temporal sectors (superotemporal and inferotemporal) and LCVA and a moderate correlation between structural progressive changes and disease progression. Previous cross-sectional studies[3,4,6] have demonstrated a correlation between retinal structural parameters and visual and neurologic dysfunction due to PD. To the best of our knowledge, this is the first longitudinal study where an association between progressive retinal changes and PD progression is observed. However, in our study only the HY scale was performed to evaluate disease progression, and the most severely physically impaired patients (with worse HY scores and faster progression) were excluded from the final statistical analysis owing to the impossibility to complete the tests. This may have caused us to underestimate the correlation between disease severity and progressive retinal thinning. We believe more longitudinal studies, including an evaluation of disease progression using other more complete and accurate scales (such as the Unified Parkinson's Disease Rating Scale [UPDRS-III]), are needed to corroborate these interesting findings.

Digital imaging technologies in ophthalmology have greatly improved in the recent years. The most recent milestone in the development of retina and choroid visualization strategies is swept-source (SS) OCT, which uses longer wavelengths than those used in SD systems (1050 nm versus 840 nm) and faster scan speed (100,000 A scans/s).[25] These new SS OCT devices provide more accurate three-dimensional images of the retina and choroid[25] and also include automated segmentation analysis of different retinal layers. Future studies applying this new SS OCT technology to neurodegenerative processes, such as multiple sclerosis and PD, will be of strong interest and may provide new information about progressive degeneration of the different retinal layers in these patients.

There were several limitations in our study. A possible important limitation was the fact that both eyes from each subject were included. Incorporating both eyes of a patient may sometimes be controversial, since minimum symmetric structural and functional alterations could have been masked and generated a percentage of dependence between measurements. However, some recent studies[26] suggest asymmetrical involvement of the retina in PD patients and recommend the incorporation of both eyes of each patient in the study. Furthermore, there is little penalty for using a two-eye analysis, even when the intereye correlation is zero. In this situation, a two-eye analysis will produce a slightly conservative estimate of precision.[27] Another possible bias was that subclinical glaucomatous eyes might have been included in the study, despite all participants (PD and controls) being evaluated for IOP levels and cup to disc ratio (by funduscopy). Since automated perimetry was not performed in this study, other glaucomatous changes could have gone unnoticed. It is possible that both groups of subjects contained subclinical glaucomatous eyes, especially the Parkinson's group, since these patients may have an increased occurrence rate of glaucoma (based on glaucomatous perimetry changes and high cup to disc ratio).[28] Despite normal tension glaucoma being difficult to detect, we believe evaluation of the cup to disc ratio in our patients decreased (although did not eliminate completely) the chances of glaucomatous damage being included in the study. Other possible causes of glaucoma were also discarded, such as past episodes of drug-induced acute closed angle glaucoma, since most reported drugs that may occasionally induce closed angle glaucoma were not prescribed to our patients[29] and no history of acute closed angle glaucoma was reported by any of the subjects in our study.

A minor limitation of our study was the fact that the Farnsworth 15D and Lanthony 15D tests, despite being largely accepted protocols, often lack sensitivity, in particular if considering the need for a deeper investigation of color discrimination alterations. In addition, the pathophysiology of this dysfunction remains poorly understood in patients with PD and has been recently linked to cognitive impairment and white-matter alterations in these patients.[30] Further studies using more complete color tests (such as the Farnsworth D100) are needed for a deeper analysis of color vision alterations in PD patients.

Specific drugs and treatments in Parkinson's disease may have also an impact in retinal thinning. Postmortem analysis of the retina of PD patients not receiving L-3,4-dihydroxyphenylalanine (L-DOPA) therapy has revealed lower retinal dopamine concentrations than controls.[31] Nevertheless, in vivo analysis of the retinal structure on L-DOPA–treated patients is scarce. A neuroprotective effect of levodopa has been suggested on the basis of RNFL measurements using Heidelberg Retina Tomograph.[32] However, such effect has not been observed with SD-OCT.[33] More longitudinal studies on the effect of dopaminergic treatment are needed to establish the role of L-DOPA in retinal structure changes.

It is well known that physiologic aging causes neuronal degeneration and reductions in most of the regional thicknesses of the peripapillary RNFL and macula, except for the temporal quadrant of the RNFL.[34] Aging is the single most significant factor influencing the clinical presentation and course and progression of PD,[35] and accelerated aging in these patients may be influencing progressive changes in RNFL and macular thickness. However, since significant progressive RNFL changes in our patients were observed in the temporal sectors, we believe that at least accelerated aging was not solely responsible for RNFL thinning in PD.

In conclusion, PD produces progressive macular thinning and axonal loss detectable by SD-OCT, together with progressive visual dysfunction in these patients. This is the first longitudinal study on progressive visual and structural changes in PD patients. We believe that future studies evaluating the correlation between progressive retinal degeneration and progression of cognitive impairment in PD would be of great importance, especially in the assessment of treatment effectiveness and protection against neuronal degeneration in these patients.

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