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The evaluation of retinal nerve fiber layer in pigment dispersion syndrome and pigmentary glaucoma using scanning laser polarimetry

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PURPOSE. *To measure the retinal nerve fiber layer thickness in patients with pigment dispersion syndrome (PDS) using scanning laser polarimetry and to compare these measurements with those of normal subjects and patients with pigmentary glaucoma (PG).*

METHODS. *Age-, sex-, and refractive error-matched subjects – 18 patients with PDS, 18 patients with PG, and 20 healthy subjects – were evaluated by scanning laser polarimetry (Nerve Fiber Analyzer [NFA] GDx). The NFA did not have a compensator for corneal polarization. One randomly selected eye from each patient was included in the statistical analysis. The NFA measurements of patients with PDS and PG and healthy subjects were compared statistically using analysis of variance, Tukey multiple comparisons, chi-square, and independent t-tests.*

RESULTS. *The mean values for average thickness, superior and inferior maximum, superior and inferior average, ellipse average thickness, and superior integral were found to be lower in the patients with PDS ($p<0.02$) and PG ($p<0.005$) compared to the normal subjects. The mean values for maximum modulation, superior ratio, inferior ratio, and superior/nasal ratio in PDS were in between those of the PG and control groups ($p>0.05$). The ellipse modulation was significantly lower in the PG group when compared to the other two groups ($p<0.03$).*

CONCLUSIONS. *Retinal nerve fiber loss is present to some extent in patients with PDS and this loss is not age or sex dependent. Parameters of modulation might be more representative of significant damage of the nerve fiber layer. (Eur J Ophthalmol 2003; 13: 377-82)*

KEY WORDS. *Pigment dispersion syndrome, Pigmentary glaucoma, Retinal nerve fiber, Scanning laser polarimetry.*

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INTRODUCTION

Pigment dispersion syndrome (PDS) is characterized by melanin pigment liberation from the iris pigment epithelium and deposition of these pigment granules throughout the anterior chamber including the corneal endothelium, anterior and posterior lens surfaces, zonules, and trabeculum. The most characteristic anterior segment findings include radial midperipheral iris transillumination defects, Krukenberg spindles, and trabecular hyperpigmentation. The pigment liberation occurs due to the mechanical rubbing between the posterior iris surface and the zonular fibers during physiologic pupillary movement (1). PDS is associated with pigmentary glaucoma (PG), a common and progressive form of secondary open-angle glaucoma (2).

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The scanning laser polarimeter is a rapid and sensitive diagnostic tool that is increasingly being used for the objective and quantitative assessment of the retinal nerve fiber layer (RNFL) (3). Scanning laser polarimetry measures the change in polarization of the laser light induced by the bi-refringent RNFL.

The purpose of this study was to measure the RNFL thickness in patients with PDS using the scanning laser polarimeter and to compare these measurements with those of normal subjects and patients with PG.

METHODS

Eighteen subjects with PDS were included in the study. Inclusion criteria for the PDS group were the presence of trabecular hyperpigmentation and Krukenberg spindle, a gonioscopically open anterior chamber angle, intraocular pressure (IOP) less than 21 mmHg on at least three different occasions, and normal results on visual field analysis. None of the subjects examined were taking antiglaucomatous medical therapy.

There were 11 men and 7 women in the PDS group with an average age of 44.7 ± 14.9 years (range 23 to 71 years). One randomly selected eye was evaluated for each patient. Ophthalmic examination included visual acuity testing including refractive error determination in spherical equivalents, IOP measurement (Goldmann tonometry), slit-lamp examination with a +90-diopter (D) lens, and gonioscopy. Patients also underwent automated visual field testing with Humphrey 30-2 full threshold program (Humphrey Allergan Instruments, San Leonardo, CA) and scanning laser polarimetry with the Nerve Fiber Analyzer (NFA GDx, version 1.0.08, Laser Diagnostic Technologies Inc, San Diego, CA).

Eighteen eyes of 18 subjects with PG were included in the study. Criteria for the diagnosis of glaucoma were the presence of trabecular hyperpigmentation and Krukenberg spindle, a gonioscopically open anterior chamber angle, IOP above 21 mmHg on at least three different occasions, and/or a reliable sign of glaucomatous visual field defect as determined by visual field testing. The PG group consisted of 10 men and 8 women with an average age of 49.9 ± 8.0 years (range 35 to 68 years). One randomly determined eye was evaluated for each subject. According to the classification described by Hodapp et al (4), 12 patients had mild, 4 had moderate, and 2 had severe glaucomatous visual field loss.

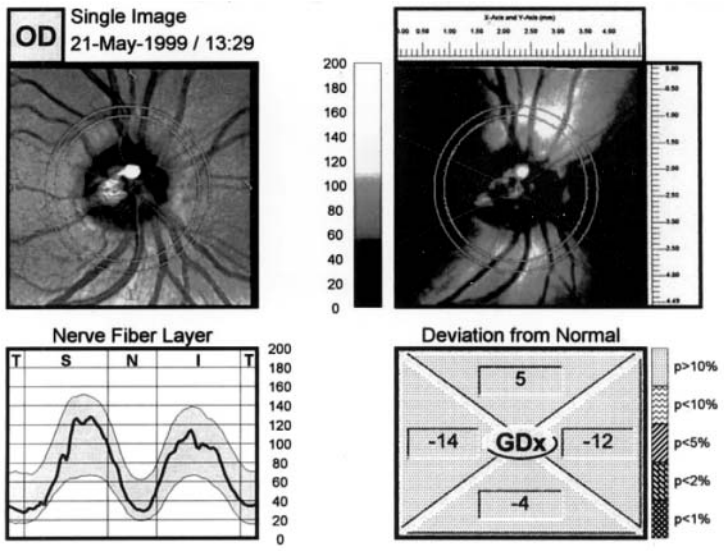
Twenty eyes of 20 subjects were included as controls. In the control group, there were 9 men and 11 women with an average age of 46.1 ± 13.5 years (range 26 to 67 years). All had normal appearing optic discs and normal results on visual field analysis with IOP less than 21 mmHg.

The NFA is a confocal scanning laser ophthalmoscope with an integrated polarimeter that measures the change in polarization of the incident light that passes through the RNFL. This technique is described in detail elsewhere (3, 5). In this study, NFA measurements were taken by the same trained examiner (M.C.M.). Three images were obtained for each eye and the image with the best quality was selected for evaluation. The measuring ellipse was positioned along a line at 1.75 disc diameters concentric with the disc margins. The measurements were taken without pupil dilatation. The NFA did not have a compensator for corneal polarization. Therefore, macular scanning was performed on all patients to determine whether corneal polarization axes had any effect on the RNFL parameters (6). Only patients without a double-hump pattern in their macular regions were included in the study. The RNFL thickness and integral values along the optic disc were calculated by NFA and used for statistical comparison.

The NFA parameters in PDS, PG, and control subjects were statistically compared using analysis of variance (ANOVA) and Tukey multiple comparison tests. The chi-square test was used to detect any differences in sex and the independent t-test was used to compare the RNFL parameters in male and female patients and in patients older and younger than 45 years in each group (mean ± SD). A p value of less than 0.05 was considered as statistically significant.

RESULTS

One-way ANOVA revealed no significant age differences among the three groups ($p>0.05$). The mean refractive error in spherical equivalents for the pigment dispersion, PG, and control groups was determined as -1.4 ± 2.1, -1.4 ± 1.5, and -1.3 ± 1.0 D, respectively. These measurements were not significantly dif-

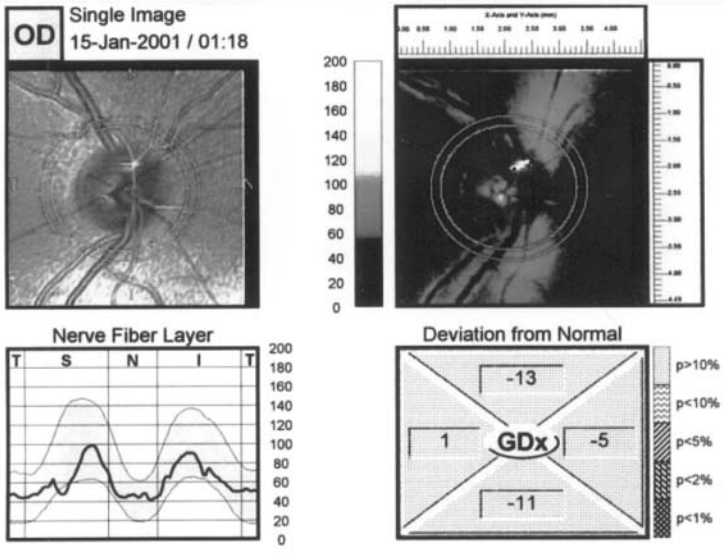


NERVE FIBER ANALYSIS

	Act. Value	Status	Probability
Symmetry	1.21	Within Normal	
Superior Ratio	3.41	Within Normal	
Inferior Ratio	2.81	Within Normal	
Superior/Nasal	3.12	Within Normal	
Max. Modulation	2.41	Within Normal	
Ellipse Modulation	3.56	Within Normal	

	Act. Value	Status	Probability
The Number	**7**		
Average Thickness	66	Within Normal	
Ellipse Average	70	Within Normal	
Superior Average	85	Within Normal	
Inferior Average	84	Within Normal	
Superior Integral	0.243	Within Normal	

Fig. 1 - *Extended nerve fiber analysis of a normal subject.*

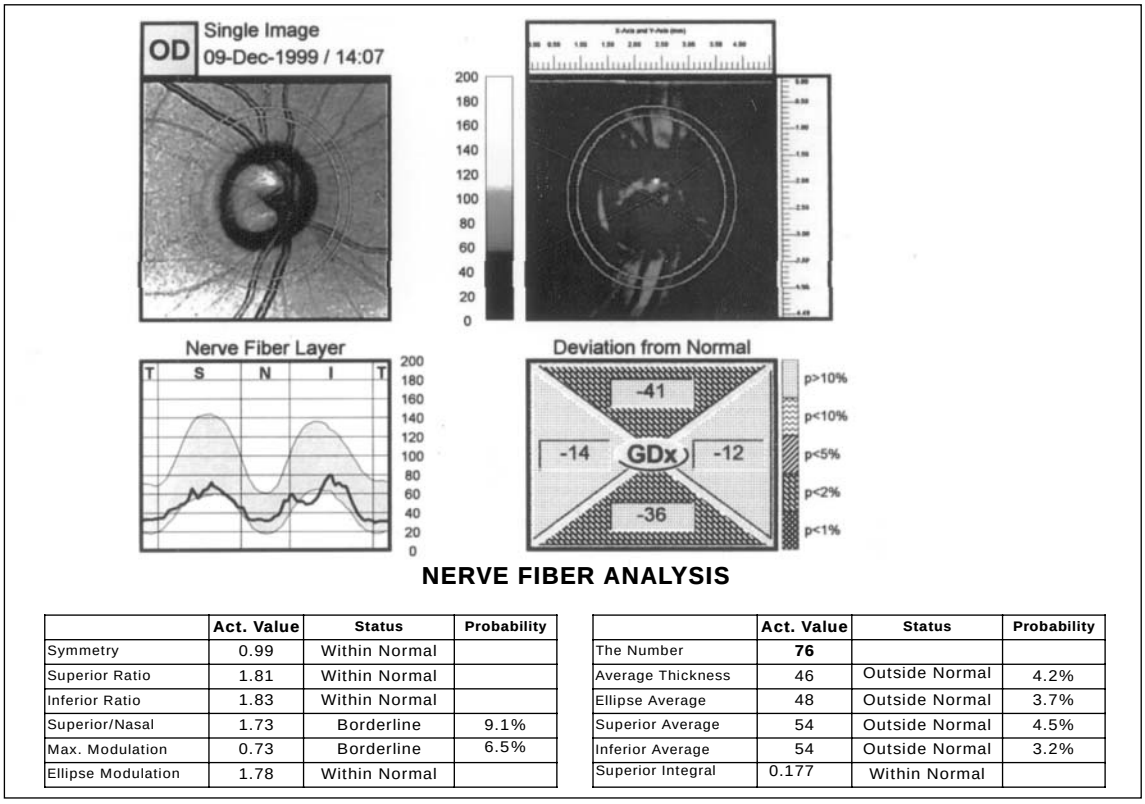


NERVE FIBER ANALYSIS

	Act. Value	Status	Probability
Symmetry	1.05	Within Normal	
Superior Ratio	1.85	Within Normal	
Inferior Ratio	1.76	Within Normal	
Superior/Nasal	2.11	Within Normal	
Max. Modulation	1.11	Within Normal	
Ellipse Modulation	1.40	Borderline	5.2%

	Act. Value	Status	Probability
The Number	**20**		
Average Thickness	60	Within Normal	
Ellipse Average	61	Within Normal	
Superior Average	68	Within Normal	
Inferior Average	69	Within Normal	
Superior Integral	0.182	Within Normal	

Fig. 2 - *Extended nerve fiber analysis of a patient with pigment dispersion syndrome demonstrating a focal defect in the supero-temporal quadrant.*



NERVE FIBER ANALYSIS

	Act. Value	Status	Probability
Symmetry	0.99	Within Normal	
Superior Ratio	1.81	Within Normal	
Inferior Ratio	1.83	Within Normal	
Superior/Nasal	1.73	Borderline	9.1%
Max. Modulation	0.73	Borderline	6.5%
Ellipse Modulation	1.78	Within Normal	

	Act. Value	Status	Probability
The Number	**76**		
Average Thickness	46	Outside Normal	4.2%
Ellipse Average	48	Outside Normal	3.7%
Superior Average	54	Outside Normal	4.5%
Inferior Average	54	Outside Normal	3.2%
Superior Integral	0.177	Within Normal	

Fig. 3 - *Extended nerve fiber analysis of a patient with pigmentary glaucoma with a very thin retinal nerve fiber layer.*

ferent as evaluated by one-way ANOVA (p>0.05).

All of the RNFL parameters except symmetry (p=0.836) were found to be significantly different among the three groups when compared using ANOVA (p<0.05). All between-group differences were tested for statistical significance using the Tukey multiple comparisons test (Tab. I). The PDS group had significantly thinner average thickness, superior and inferior maximum, superior and inferior average, ellipse average thickness, and superior integral measurements when compared to normal subjects (p<0.02). Figures 1, 2, and 3 show extended NFA analysis of a healthy subject, a patient with PDS, and a patient with PG.

The RNFL parameters of the study groups were further compared with regard to sex and age. The average age of 11 men in the PDS group was 45.4 (±15.0) years and of 7 women was 43.6 (±15.9) years. These values were not significantly different from each other (p=0.81). In this group, none of the GDx parameters, except the superior average thickness, were different for the male subjects when compared with the female subjects using the independent t-test (p>0.05). The superior average parameter was significantly thinner in the male subjects (p=0.04).

The average age of 10 men in the PG group was 49.5 (±6.2) years and of 8 women was 50.4 (±10.2) years. These values were not significantly different from each other (p=0.83). In this group, there were no significant differences in 14 GDx parameters between male and female subjects using the independent t-test (p>0.05).

The average age of 9 men in the control group was 38.4 (±12.3) years and of 11 women was 52.3 (±11.4) years. Statistical analysis revealed a significantly higher mean age for women when compared to the men (p<0.05). In this group, only the ellipse average parameter was found to be thicker in men when compared to women (p<0.05).

When 9 subjects in the PDS group younger than 45 years of age were compared with the 9 subjects older than 45 years, only superior/nasal ratio and maximum modulation (p<0.05) were found to be significantly different. The younger (<45 years) population had higher values for the two parameters found to be different.

When 6 subjects in the PG group younger than 45 years of age were compared with the 12 subjects old-

TABLE I - RETINAL NERVE FIBER LAYER PARAMETERS IN PATIENTS WITH PIGMENT DISPERSION SYNDROME (PDS), PIGMENTARY GLAUCOMA (PG), AND CONTROLS (MEAN ± SD) AND THE STATISTICAL SIGNIFICANCE OF GROUP MEAN DIFFERENCES AS EVALUATED BY TUKEY MULTIPLE COMPARISONS TEST

Parameter	Normal	PDS	PG	PDS vs. normal (p)	PG vs. normal (p)	PDS vs. PG (p)
Average thickness (µm)	68.1±8.7	58.1±6.6	57.2±7.7	0.001	0.000	0.929
Ellipse average (µm)	71.9±9.3	61.6±6.9	58.9±8.4	0.001	0.000	0.603
Superior average (µm)	80.0±12.5	70.2±8.4	64.8±10.2	0.018	0.000	0.279
Inferior average (µm)	86.1±8.9	70.9±10.5	66.6±11.7	0.000	0.000	0.415
Superior maximum (µm)	95.0±13.1	78.7±9.0	73.9±14.1	0.000	0.000	0.488
Inferior maximum (µm)	96.5±9.9	81.5±14.6	73.6±11.7	0.001	0.000	0.132
Superior integral (mm^2)	0.22±0.03	0.19±0.02	0.18±0.03	0.006	0.000	0.320
Maximum modulation	1.6±0.5	1.3±0.4	1.0±0.4	0.098	0.000	0.109
Ellipse modulation	2.6±0.7	2.5±0.6	1.8±0.8	0.689	0.002	0.020
Number	14.6±5.9	26.2±14.6	44.0±25.6	0.100	0.000	0.008
Superior ratio	2.4±0.5	2.1±0.4	1.9±0.5	0.151	0.004	0.342
Inferior ratio	2.4±0.5	2.2±0.5	1.8±0.3	0.182	0.000	0.077
Superior/nasal	2.1±0.4	1.9±0.3	1.7±0.4	0.169	0.001	0.170

er than 45 years, all of the GDx parameters were found to be similar in each group ($p>0.05$).

When 10 subjects in the control group younger than 45 years of age were compared with the 10 subjects older than 45 years, none of the GDx parameters except symmetry ($p<0.05$) were found to be significantly different. However, the two groups had significantly different mean refractive error in spherical equivalents, with the younger group exhibiting higher myopia (mean -2.0 D) than the older group (mean -0.7 D) ($p<0.005$).

DISCUSSION

PDS affects the relatively young adult population in the third and fourth decades. In a recent study, the estimated prevalence of PDS in a population undergoing glaucoma screening was determined as 2.45% (7). PDS is thought to be inherited in an autosomal dominant pattern with different phenotypic expression and the responsible gene is mapped to the telomeric end of the long arm of chromosome 7 (7q35-q36) (8). It is seen more commonly in males and in myopic individuals (7, 9). PDS is associated with PG that is believed to develop due to the obstruction of the trabecular meshwork by the released pigment granules (10, 11). PG develops in the setting of active pigment dispersion in the anterior chamber with resultant trabecular obstruction (10). Continued pigment dispersion results in irreversible degeneration of the trabeculum, persistent IOP elevation, and progressive ganglion cell damage. Although the exact frequency of progression of the syndrome into glaucoma is not known, estimates from previous studies range from 20% to 50% (2, 9, 12). Consequently, early detection of glaucomatous progression in young patients with PDS is especially important to prevent permanent loss of sight.

In this study we compared the RNFL thickness parameters of subjects with PDS and PG. As expected, all of the RNFL thickness parameters were significantly lower in the PG population when compared with the normal population. Interestingly, certain RNFL parameters – namely, the average thickness, ellipse average, superior maximum, inferior maximum, superior average, inferior average thickness, and superior integral values – were also considerably lower in the PDS group compared with the normal population despite the fact that none of the subjects with PDS had elevated IOP readings or glaucomatous visual field defects ($p<0.05$). These findings suggest the presence of early RNFL loss in the subjects with PDS. In the absence of sustained elevations of IOP, it might be possible that these subjects develop spontaneous or exercise-related intermittent high IOP that can not be detected during routine ophthalmologic examination. Intermittent IOP elevations have been described in the

initial stages of this disease when the trabeculum is still able to compensate for the active melanin pigment dispersion (10). The intermittent nature of high IOP might be responsible for the slight RNFL loss in the subjects with PDS. In a study by Farrar et al (9), risk factors associated with glaucomatous progression in patients with PDS were identified as male gender, black race, severe myopia, and the presence of Krukenberg spindles. Another study by Küchle et al (13) demonstrated that the number of aqueous granules as measured by laser flare-cell meter was correlated with the degree of Krukenberg spindle. In our study, all of the patients with PDS had Krukenberg spindles and therefore our population might be representative of the PDS subjects with more active anterior chamber pigment dispersion and a more severe trabecular obstruction and degeneration. The RNFL loss might not be present in patients with PDS with less or arrested pigment dispersion.

This study also demonstrated that the RNFL loss was not significantly different in men compared to women. The only parameter determined to be different between the men and the women was the superior average thickness, with men having thinner values. As stated previously, male sex is also a risk factor for glaucomatous progression in this population, probably due to anatomic predisposing factors for pigment dispersion such as deeper absolute and relative anterior chamber depths (14). However, this study has failed to show definite evidence in terms of nerve fiber layer damage to support the validity of this clinical risk factor.

Age was not found to be a risk factor for RNFL loss in PDS subjects. Among GDx parameters only the superior/nasal ratio and the maximum modulation were lower in the older population compared to the younger population in the PDS group. In conclusion, the results obtained in this study demonstrate that loss of RNFL is present in patients with PDS. However, men and older patients are not particularly prone to developing nerve fiber layer defects. Subjects with PDS might be developing RNFL defects at a very early stage in the course of this disease, even before overt IOP elevations and glaucomatous visual field defects become evident. In the follow-up of these subjects, serial RNFL measurements using the NFA might prove useful in demonstrating early progression of RNFL loss and in prompt initiation of antiglaucomatous therapy to prevent further nerve fiber layer damage.

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