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CLINICAL STUDY

Characteristics of patients with a localized retinal nerve fiber layer defect and normal optic disc appearance

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Abstract

Purpose **To investigate the characteristics of patients with a localized retinal nerve fiber layer (RNFL) defect and normal optic disc appearance compared with normal tension glaucoma (NTG) patients.**

Methods **A total of 40 patients with an unchanged RNFL defect for more than 5 years and normal optic disc appearance, who were presumed as non-glaucomatous patients, were enrolled (group A). We recruited 40 age-matched patients with NTG (group B). On the RNFL photographs, we evaluated angles of RNFL defects. Angle α and β were the angles made by the line 'L' from the center of the fovea to the disc center and the lines 'A' and 'B' from the disc center to the disc margin where the proximal and the distal border of the defect met, respectively. Angle θ was the angular width of the defect. Angle γ was the angle made by lines 'L' and 'R', which divides angle θ into a 2:1 ratio from line 'A' to line 'B'. We compared systemic diseases, baseline IOP, and location and angles of the RNFL defects between the two groups.**

Results **Systemic diseases and superotemporal RNFL defects in group A were significantly greater than those in group B ($P<0.001$). Angle α was greater in group A, but angle β, θ, and γ were smaller in group A ($P<0.05$).**

Conclusion **If the patients with a superotemporal RNFL defect and normal optic disc appearance had systemic diseases and distal borders of the defects are closer to the macula, glaucoma is less likely.**

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Keywords: retinal nerve fiber layer defect; no change of defect; red-free fundus photography; preperimetric glaucoma; normal tension glaucoma

Introduction

Since the significance of retinal nerve fiber layer (RNFL) evaluation in the early diagnosis of glaucoma was described by Hoyt and Newman,[1] several investigators have demonstrated that RNFL defects may precede the onset of glaucomatous field loss.[2,3] Some ophthalmologists believe that localized RNFL defects are one of the most sensitive parameters in the detection of glaucoma.[4] However, glaucoma is defined as progressive optic neuropathy, which is characterized by the loss of retinal ganglion cells through disruptions of axoplasmic flow in the lamina cribrosa. RNFL defects are not only caused by axoplasmic flow disruptions in the retinal ganglion cells but can also be induced by vascular accidents or some other events in RNFL. RNFL defects are not a pathognomonic sign of glaucoma. They have been detected in other ocular diseases, including nonarteritic anterior ischemic optic neuropathy, toxoplasmotic retinochoroiditis, optic neuritis, long-standing papilledema, optic disc drusen, and pituitary gland tumors.[5] Some reports have demonstrated that RNFL defects may be a common finding in diabetic patients with diabetic retinopathy,[6] and the RNFL thickness in patients with chronic renal failure without diabetes mellitus (DM) was reduced significantly.[7] Some authors also have reported localized RNFL defects after retinal cotton wool

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spots.[8–11] According to previous reports, some of these RNFL defects have presented corresponding visual field (VF) defects and detectable changes in optical coherence tomography as RNFL defects in glaucoma have.

As the importance of early detection of glaucomatous damage has been emphasized and the ability to quantitatively evaluate RNFL has improved, many patients with a RNFL defect have been detected. Even though most localized RNFL defects were associated with neuroretinal rim thinning, notching, or vertical cup enlargement, some localized RNFL defects were associated with normal disc appearance. We have experienced some localized RNFL defects with normal disc appearance, which have not progressed for years. Therefore, we assumed that a localized RNFL defect with normal disc appearance could be caused by conditions other than glaucoma. In this study, we investigated the characteristics of patients with a RNFL defect and normal optic disc appearance compared with normal tension glaucoma (NTG) patients.

Materials and methods

We retrospectively reviewed the medical records of patients with a localized RNFL defect at the Department of Ophthalmology of Samsung Medical Center from May 2001 to November 2010. The methods applied in this study adhered to the tenets of the Declaration of Helsinki for the use of human subjects in biomedical research and this investigation was approved by Institutional Review Board of Samsung Medical Center, Seoul, Korea.

At initial work-up, each patients received a comprehensive ophthalmic examination, including a review of medical history, measurement of best corrected visual acuity, slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated funduscopic examination, disc stereophotography, RNFL photograph, VF examination, and central corneal thickness (CCT) examination. Red-free fundus photographs of RNFL and disc stereophotographs were taken with a TRC-50IX (Topcon Corp., Tokyo, Japan) fundus camera after maximum pupil dilation. The VF tests were conducted using the 30-2 strategies program with a Humphrey visual field analyzer (Model 750I; Humphrey Instruments, Inc., San Leandro, CA, USA). Some patients performed confocal scanning laser ophthalmoscopy (HRT2-Heidelberg Retina Tomograph; Heidelberg Engineering, Heidelberg, Germany).

A diagnosis of NTG was made when a patient with an intraocular pressure (unadjusted and adjusted IOP) of 21 mm Hg or less without treatment, had findings of glaucomatous optic disc damage and corresponding VF defects, an open angle observed by gonioscopic examination, and no underlying cause for the optic disc damage aside from glaucoma. A VF test were regarded as abnormal if the following criteria were met on at least two consecutive VF examinations with acceptable reliability standards: (1) an abnormal glaucoma hemifield test result (borderline findings were not regarded as abnormal), (2) at least three contiguous non-edge points (allowing two nasal step-edge points) via Humphrey 30-2 standard automated perimetry with $P<0.5$ on the pattern standard plot and at least one point with $P<0.01$. The location and pattern of the defect had to be consistent between the two consecutive VF examinations, and the glaucomatous optic disc and RNFL damage had to be consistent with the VF abnormality.[12] A reliable VF was required to have a fixation loss of less than 20% and a false-positive and false-negative rate of 15% or less.

We measured baseline IOP in the morning (0900 hours to 1200 hours) on one examination day and in the afternoon (1300 hours to 1700 hours) on another day with less than a 1-month interval between measurements, both after a 4-week washout period. IOP was measured by a single glaucoma specialist (CK), and the mean of three measurements was recorded for each eye. Baseline IOP was adjusted by 2.5 mm Hg for every 50 μm that the CCT deviated from 530 μm,[13] and this adjusted IOP was analyzed to minimize the confounding effects of CCT on IOP.

Study groups

Patients (group A) had to meet the following criteria: (1) IOP lesser than 21 mm Hg, (2) normal optic disc appearance without evidence of thinning, notching, or localized pallor, and (3) an unchanged localized RNFL defect for more than 5 years. We defined the change of RNFL defect by the widening of the defect as measured in fundus photographs. Serial VF examination results and stereoscopic disc photos were also analyzed for possible change. The optic disc and RNFL photographs and VF examination were evaluated by two observers (CK and JK) and each observer was masked to the subject's identity and the other test results. Subjects in which there was a disagreement between observers were excluded. Forty eyes of 40 patients were enrolled into group A in this retrospective study. Among them, 34 eyes (85%) were performed HRT and the results showed within normal limit of the optic disc.

We recruited 40 eyes of 40 NTG patients with a localized RNFL defect, who were matched with patients in group A based on their age at diagnosis (group B). The ages of the subjects in group B were within 3 years of the ages of the participants in group A. Mean deviation of all eyes was more than -12 dB. All of them were performed HRT, which showed results outside normal limit of the optic discs.

The exclusion criteria were as follows: (1) previous ocular pathology including diabetic retinopathy that could affect the VF test, (2) previous systemic disease that could affect the VF test and optic disc appearance, and (3) abnormal optic disc appearance, such as high myopia (spherical equivalent < -6.0 D) and tilted disc, which could interfere with diagnosis.

Clinical data and parameters of RNFL

β-zone parapapillary atrophy (PPA) was defined as the central zone of PPA characterized by chorioretinalatrophy with visible large choroidal vessels and sclera. If they showed only a peripheral zone (zone α) of PPA with irregular hyperpigmentation, hypopigmentation and a peripheral scleral ring, they were not considered as β-zone PPA.

Localized RNFL defects were defined as a dark wedge-shaped area with a connecting optic disc border. On the RNFL photographs, we measured the angle of a localized RNFL defect using reference line 'L', which is the line from the center of the fovea to the disc center using an image analysis program (Image J software version 1.38; Java software program by NIH, Bethesda, MD, USA). Angle α was the angle made by line 'L' and line 'A' from the disc center to the disc margin, where the proximal border of the RNFL defect met; angle β was the angle made by line 'L' and line 'B' from the disc center to the disc margin, where the distal border of the RNFL defect met. Angle θ was the angular width of the defect and the angle made by line 'A' and line 'B'. We arbitrarily defined angle γ to more accurately reflect the initial location of the RNFL defect. Angle γ was the angle made by lines 'L' and 'R', which divides angle θ into a 2 : 1 ratio from line 'A' to line 'B'. These are illustrated in Figure 1. To prevent examiner bias, two ophthalmologists (JL, JK) made two measurements on different days without any information. Reproducibility was assessed using the intraclass correlation coefficient (ICC).

We compared systemic diseases, baseline IOP, location of the RNFL defect, angle α, angle β, angle θ, angle $\gamma 1$, and angle $\gamma 2$ between the two groups. Statistical analysis was done using SPSS for Windows (version 12.0.0; SPSS, Chicago, IL, USA). A *P*-value of less than 0.05 was accepted as statistically significant.

Results

The mean follow-up period was 76.8 ± 25.0 months. Table 1 provides descriptive statistics for demographic and ophthalmic measurements. The mean age (53.8 ± 9.6 *vs* 54.3 ± 9.9, $P = 0.81$), age distribution, and percentage of male patients did not differ between the two groups. Unadjusted baseline IOPs of group A and group B were 14.5 ± 3.5 mm Hg and 16.0 ± 3.0 mm Hg, respectively. The mean CCTs of group A and group B were 537.9 ± 32.6 mm and 532.43 ± 38.58 mm, respectively, and adjusted baseline IOPs of group A and group B were 15.2 ± 3.4 mm Hg and 16.7 ± 3.9 mm Hg, respectively. The mean CCT did not differ between the two groups ($P = 0.543$, independent *t*-test). Unadjusted baseline IOP and adjusted baseline IOP were higher in group B than in group A but were not statistically significantly different ($P = 0.05$ and $P = 0.09$, independent *t*-test). Systemic diseases differed significantly between the two groups (62.5% in group A *vs* 25% in group B, $P = 0.001$). The number of patients with DM was larger in group A than in group B (27.5% *vs* 7.5%, $P = 0.019$, chi- square test) and patients with hypertension was larger in group A than in group B (47.5% and 22.5%, $P = 0.019$, chi-square test). Any systemic disease except for DM and hypertension was not detected in each group.

The frequency of β-zone PPA did not differ between the two groups (52.5% in group A *vs* 65.0% in group B, $P = 0.313$). Analyses of localized RNFL defects are shown

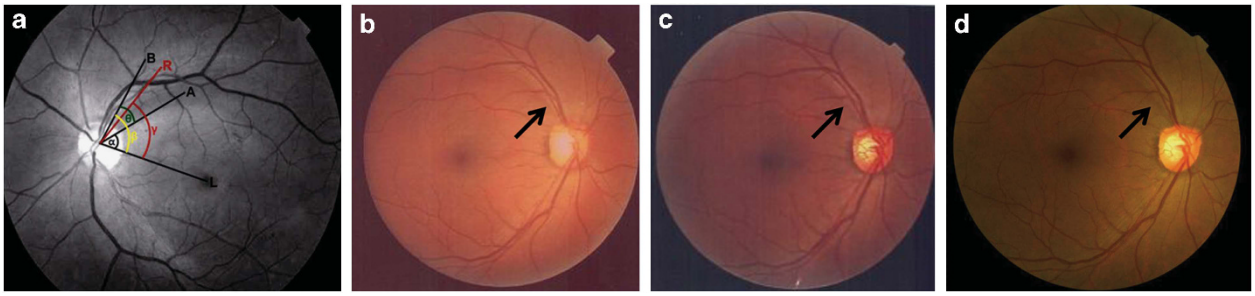

Figure 1 Measurements of a localized RNFL defect from the RNFL photograph (a) and fundus photos of a patients in group A (b–d). (a) Reference line 'L' is the line from the center of the fovea to the disc center. Angle α and β were the angles made by the line 'L' from the center of the fovea to the disc center and the lines 'A' and 'B' from the disc center to the disc margin where the proximal and the distal border of the defect met, respectively. Angle θ was the angular width of the defect. Angle γ was the angle made by lines 'L' and 'R', which divides angle θ into a 2 : 1 ratio from line 'A' to line 'B'. Fundus photographs shows no progression of the RNFL defect 10 years (d) and 2 years (c) after initial visit (b).

Table 1 Demographics and descriptive statistics for ophthalmic measurements

Variables	*Group A* N = *40*	*Group B* N = *40*	P
Age (years)	53.8 ± 9.6	54.3 ± 9.9	0.81[a]
≤45	5	6	
>45	17	14	
>55	13	15	
>65	5	5	
Male, *n* (%)	26 (65.0%)	21 (52.5%)	0.313[b]
Systemic disease, n *(%)*	25 (62.5%)	10 (25%)	0.001[b]
DM	11 (27.5%)	3 (7.5%)	0.019[b]
Hypertension	19 (47.5%)	9 (22.5%)	0.019[b]
Right eye, *n* (%)	21 (52.5%)	21 (52.5%)	1[b]
β-zone PPA, *n* (%)	21 (52.5%)	26 (65%)	0.313[b]
CCT (mm)	537.9 ± 32.6	532.43 ± 38.58	0.543[a]
Baseline IOP (mm Hg)			
Unadjusted	14.5 ± 3.5	16.0 ± 3.5	0.05[a]
Adjusted	15.2 ± 3.4	16.7 ± 3.0	0.09[a]

Abbreviations: DM, diabetes mellitus; N, number of eyes; PPA, parapapillary atrophy.
[a] *P*-value based on independent *t*-test.
[b] *P*-value based on chi-square test.

Table 2 Analysis of RNFL defects

Variables	*Group A* N = *40*	*Group B* N = *40*	P
Number of ST RNFL defects, *n* (%)	31 (77.5%)	11 (27.5%)	<0.001[a]
Angle *α*	60.2 ± 18.7	44.3 ± 14.4	<0.001[b]
Angle *β*	67.9 ± 19.8	87.8 ± 14.4	<0.001[b]
Angle *θ*	7.7 ± 6.5	43.5 ± 19.2	<0.001[b]
Angle *γ*	65.3 ± 19.2	73.3 ± 11.2	0.026[b]

Abbreviations: N, number of eyes.
[a] *P*-value based on chi-square test.
[b] *P*-value based on independent *t*-test.

in Table 2 and Figure 2. The superotemporal RNFL defect in group A was much more than that in group B (77.5% *vs* 27.5%, $P<0.001$). Angle *α* was significantly greater in group A (60.2 ± 18.9° *vs* 44.3 ± 14.4°, $P<0.001$). Angle *β* and angle *θ* were smaller in group A (67.9 ± 19.8° *vs* 87.8 ± 14.4°, 7.7 ± 6.5° *vs* 43.5 ± 19.2°, $P<0.001$). Angle *γ* was smaller in group A (65.3 ± 19.2° *vs* 73.3 ± 11.2°, $P=0.026$). The number of the eyes with an inferotemporal RNFL defect in group A and group B were 9 and 29, respectively. Angle *β*, angle *θ*, and angle *γ* in eyes showing an inferotemporal defect were smaller in group A than group B (median; 52.96° *vs* 85.47°, 6.49° *vs* 49.8°, 48.12° *vs* 71.80°, $P<0.05$, Mann–Whitney *U*-test). Angle *α* in eyes showing an inferotemporal defect was not deferent between two groups (meridian; 41.2 *vs* 48.7, 45.7 *vs* 65.2, $P=0.325$ and 0.058, Mann–Whitney *U*-test) (Table 3). The intraobserver variability in measurement of angle *α* and angle *β* were good (angle *α* ICC = 0.985, angle *β* ICC = 0.991 by JL; angle *α* ICC = 0.993, angle *β* ICC = 0.994 by JK). The interobserver agreement of both angle were good (angle *α* ICC = 0.975, angle *β* ICC = 0.975).

Discussion

In the present study, we presumed that an unchanged localized RNFL defect with normal disc appearance could be caused by conditions other than glaucoma. The RNFL defect in group B, NTG patients group, was mainly located at the inferotemporal retina (77.5%). This result is consistent with the findings of other NTG studies. In one report, 80.4% of localized defects were located at the inferotemporal meridian, followed by the superotemporal meridian (54.2%).[13] Suh *et al*[14] reported previously that 92.3% of eyes with NTG, which had progressive RNFL defects, showed RNFL defects at the inferotemporal retina and 76.9% of eyes had RNFL defects only at the inferotemporal retina. They suggested that this location is the most susceptible to glaucomatous damage. In this study, the inferotemporal RNFL defects in group A, which were presumed to be the non-glaucomatous patients group, were found in only 22.5% of the 40 eyes, which differs significantly from previous results of NTG studies. They were mainly located at the superotemporal retina (77.5%). It suggests that the cause of a localized RNFL defect in group A may differ from that of glaucoma, because the susceptible location was different, as nonarteritic anterior ischemic optic neuropathy generally appears in the upper half of the disc.

Hayreh and Jonas[15] previously reported that chronic arterial hypertension and atherosclerosis result in localized RNFL defects without altering the size and shape of the neuroretinal rim via experimental studies of Rhesus monkeys with normal IOP. Because arterial hypertension and artherosclerosis cause vascular accidents or act as a risk factor for their development,[16–18] it suggests that vascular accidents or related events may lead to localized RNFL defects. It is also supported by the fact that RNFL defects are common in patients with early diabetic retinopathy and by the fact that RNFL defects are frequently followed by cotton wool spots.[6,8–11] In this study, systemic diseases, such as DM and hypertension, were significantly more frequent in group A than in group B (62.5% *vs* 25%). These conditions may affect RNFL in group A and it may cause localized RNFL defects in many of the patients in group A. It appears likely that a superotemporal RNFL defect in patients with systemic diseases may be caused by vascular accidents and related events, rather than glaucoma.

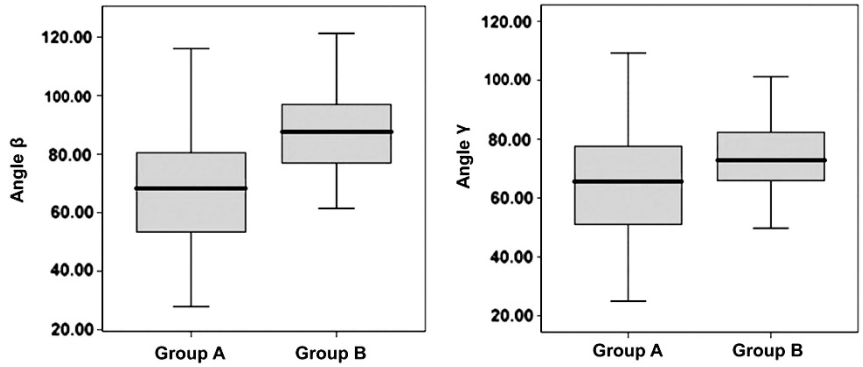

Figure 2 Distribution of angle β and angle γ. The horizontal line of the box represents the average of angle β and angle γ.

Table 3 Analysis of inferotemporal RNFL defects in group A and B

Variables	*Group A* N = *9*	*Group B* N = *29*	P
Angle α	41.2 (37.0, 66.25)	48.7 (32.4, 47.8)	$<0.311^a$
Angle β	52.96 (46.5, 72.5)	85.47 (72.6, 100.5)	$<0.001^a$
Angle θ	6.5 (4.4, 11.4)	49.8 (33.1, 60.8)	$<0.001^a$
Angle γ	48.12 (43.7, 70.4)	71.8 (64.9, 77.4)	0.005^a

Abbreviations: N, number of eyes.
[a] *P*-value based on Mann–Whitney *U*-test.

In this study, unadjusted and adjusted baseline IOP revealed a higher tendency in group B than in group A, even though they were not statistically significant. This is consistent with a previous report that the IOP of NTG tends to be higher than that in the general healthy population.[19]

In our study, angle θ was smaller in group A than in group B. In NTG, the greater the progression is, the greater the angular width (angle θ) will be. Therefore, angle θ is a variable factor. We attempted to find the initial location of an RNFL defect to compare the RNFL defect in group A with the glaucomatous RNFL defect in group B. In a report regarding the patterns of progression of RNFL defects in NTG,[14] the widening of the defect away from the macula, corresponding to a change in angle β, occurs in 12.5% of the 65 studied NTG eyes. In the rest of the eyes, angle β was unchanged. Furthermore, the mean angular change in angle β was smaller than that of angle α ($6.4 \pm 4.1^\circ$ in angle α *vs* $3.4 \pm 2.1^\circ$ in angle β). Therefore, angle β should have a role in the determination of the initial location of an RNFL defect, regardless of stage. In this study, angle β was significantly smaller in group A.

To consider some patients in which angle β might be changed, we measured angle γ. As we have mentioned above, RNFL defects that changed angle β was 12.5%, and 61.5% of eyes revealed a change in angle α in the report by Suh *et al*.[14] Considering the ratio of the changes in angle α and angle β, we arbitrarily defined angle γ to more accurately reflect the initial location of the RNFL defect. Angle γ was the angle made by lines 'L' and 'R', which divides angle θ into a 2 : 1 ratio from line 'A' to line 'B'. Angle γ was smaller in group A, as was angle β. Therefore, it can be stated that the distal border or initial location of the defect was closer to the macula in group A than in group B, regardless of the NTG stage in group B. Additionally, we compared the angles in eyes showing an inferotemporal defects in group A with those in group B. The number of the eyes with an inferotemporal RNFL defect in group A was 9. Angle β and angle γ in eyes showing an inferotemporal defect were also smaller in group A than group B. Therefore, it suggests that the distal border of the defect in group A was also closer to the macula, even though an RNFL defect was located at the inferotemporal retina.

The possible limitations of this study are biases due to its retrospective nature and small sample size. A significant factor associated with RNFL defect in each groups may not be discovered. Furthermore, although all patients had been followed for 5 years minimally and the mean follow-up period was 76.8 ± 25.0 months, the probability that extremely early NTG patients might be included in group A cannot be completely excluded. Longitudinal analysis of a larger population would be required to validate this observation. However, despite those limitations, clearly different characteristics were observed in group A. Among them, 62.5% had systemic diseases. This rate in group A was greater than that in the NTG population, despite the fact that hypertension and DM are risk factors for NTG. In addition, 77.5% of them had a superotemporal defect. Therefore, we suggest that group A may be representative of patients who only have a localized RNFL defect, not glaucoma.

In conclusion, we enrolled the patients, who had an unchanged localized RNFL defect for more than 5 years

and whose optic disc were normal, in group A. They also showed results within normal limit of the optic disc on HRT. They had more systemic diseases and their RNFL defects were located more in a superotemporal retina and the distal borders of that were closer to the macula compared with NTG patients. This suggests that if the patients with a superotemporal RNFL defect and normal disc appearance have systemic diseases and distal borders of the defects are closer to the macula, glaucoma is less likely. This information may provide important insights into identifying patients who should not be treated.

Summary

What was known before

- Many ophthalmologists believed that localized retinal nerve fiber layer (RNFL) defects are one of the most sensitive parameters in the detection of glaucoma.

What this study adds

- We investigated the characteristics of patients with a RNFL defect and normal optic disc appearance compared with normal tension glaucoma (NTG) patients.
- We observed characteristics different from NTG.
- We think this information may provide insights to discriminate patients with a RNFL defect.

Conflict of interest

The authors declare no conflict of interest.

References

1 Hoyt WF, Newman NM. The earliest observable defect in glaucoma? *Lancet* 1972; **1**: 692–693.
2 Sommer A, Miller NR, Pollack I, Maumenee AE, George T. The nerve fiber layer in the diagnosis of glaucoma. *Arch Ophthalmol* 1977; **95**: 2149–2156.
3 Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol* 1989; **107**: 453–464.
4 Quigley HA, Reacher M, Katz J, Strahlman E, Gilbert D, Scott R. Quantitative grading of nerve fiber layer photographs. *Ophthalmology* 1993; **100**: 1800–1807.
5 Jonas JB, Schiro D. Localized retinal nerve fiber layer defects in nonglaucomatous optic nerve atrophy. *Graefes Arch Clin Exp Ophthalmol* 1994; **232**: 759–760.
6 Chihara E, Matsuoka T, Ogura Y, Matsumura M. Retinal nerve fiber layer defect as an early manifestation of diabetic retinopathy. *Ophthalmology* 1993; **100**: 1147–1151.
7 Demir MN, Eksioglu U, Altay M, Tok O, Yilmaz FG, Acar MA *et al*. Retinal nerve fiber layer thickness in chronic renal failure without diabetes mellitus. *Eur J Ophthalmol* 2009; **19**: 1034–1038.
8 Alencar LM, Medeiros FA, Weinreb R. Progressive localized retinal nerve fiber layer loss following a retinal cotton wool spot. *Semin Ophthalmol* 2007; **22**: 103–104.
9 Alencar LP, Konno F, Raiza AC, Susanna R Jr. Retinal nerve fiber layer defect in a patient with healthy neuroretinal rim. *Clinics* 2007; **62**: 197–198.
10 Chaum E, Drewry RD, Ware GT, Charles S. Nerve fiber bundle visual field defect resulting from a giant peripapillary cotton-wool spot. *J Neuroophthalmol* 2001; **21**: 276–277.
11 Chihara E, Honda Y. Topographic changes in the optic disc in eyes with cotton-wool spots and primary open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1991; **229**: 13–18.
12 Anderson DR, Patella VM. *Automated Static Perimetry* 2nd ed. Mosby: St Louis, 1999.
13 Leung CK, Choi N, Weinreb RN, Liu S, Ye C, Liu L *et al*. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: pattern of RNFL defects in glaucoma. *Ophthalmology* 2010; **117**: 2337–2344.
14 Suh MH, Kim DM, Kim YK, Kim TW, Park KH. Patterns of progression of localized retinal nerve fibre layer defect on red-free fundus photographs in normal-tension glaucoma. *Eye* 2010; **24**: 857–863.
15 Hayreh SS, Jonas JB. Appearance of the optic disk and retinal nerve fiber layer in atherosclerosis and arterial hypertension: an experimental study in rhesus monkeys. *Am J Ophthalmol* 2000; **130**: 91–96.
16 Hayreh SS, Piegors DJ, Heistad DD. Serotonin-induced constriction of ocular arteries in atherosclerotic monkeys. Implications for ischemic disorders of the retina and optic nerve head. *Arch Ophthalmol* 1997; **115**: 220–228.
17 Hayreh SS. Retinal and optic nerve head ischemic disorders and atherosclerosis: role of serotonin. *Prog Retin Eye Res* 1999; **18**: 191–221.
18 Hayreh SS. Duke-elder lecture. Systemic arterial blood pressure and the eye. *Eye* 1996; **10**(Part 1): 5–28.
19 Gramer E, Leydhecker W. [Glaucoma without ocular hypertension. A clinical study]. *Klin Monbl Augenheilkd* 1985; **186**: 262–267.