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Nerve fiber layer assessment with scanning laser polarimetry in glaucoma patients and glaucoma suspects

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PURPOSE. *To investigate whether scanning laser polarimeter can differentiate glaucoma and suspected glaucoma patients from normals.*

METHODS. *Polarimetric measurements were obtained using the nerve fiber analyzer (NFA)-I from 80 eyes of patients with glaucoma with mostly moderate glaucomatous optic nerve damage (37 eyes with primary open angle glaucoma, 21 with normal tension glaucoma, 17 with pseudoexfoliative glaucoma, 3 with angle closure glaucoma, and 2 with juvenile glaucoma), 53 eyes of patients suspected of glaucoma based on disc appearance, and from age-matched healthy volunteers as control groups. Ratios (superior/nasal, inferior/nasal, superior/inferior) were used for assessing nerve fiber layer (NFL) thickness. Student's t-test and linear regression analysis were used for statistical analysis.*

RESULTS. *Both the glaucoma patients and glaucoma suspects had significantly lower NFL ratios (mean S/N 2.34 ± 0.47, I/N 2.46 ± 0.52, S/I 0.94 ± 0.18) than the control groups (respectively 2.88 ± 0.48, 2.88 ± 0.48, 1.00 ± 0.13) ($p<0.05$). There was an ample overlap between the patient groups and the normals. The superior and inferior NFL ratios in glaucoma patients gradually decreased as the mean defect in visual field increased (linear regression analysis, $p<0.05$).*

CONCLUSIONS. *The NFL of glaucomatous eyes and eyes suspected of glaucoma based on disc appearance was significantly less thick than normals. NFA-I detects pathological abnormalities in some patients with glaucomatous optic nerve damage and normal visual fields as measured by conventional achromatic computerized perimetry. NFA-I, however, is unable to distinguish these patients from normals, at least using these parameters, because of the considerable overlap. (Eur J Ophthalmol 2001; 11: 139-44)*

KEY WORDS. *Scanning laser polarimetry, Glaucoma, Glaucoma suspects*

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INTRODUCTION

The retinal nerve fiber layer (NFL) is the innermost layer of the retina and consists of ganglion cell axons which are the target cells in glaucoma. Axonal loss in glaucoma causes visual field loss which, however, is only detected when a considerable amount of the NFL has been lost (1). Therefore, assessment of the NFL has become the basic method for the early detection and follow-up of glaucoma. The first method for examining the NFL was red-free ophthalmoscopy with photography (2). Measurement of juxtapapillary NFL with optic nerve head analyzers followed (3) but unfortunately, none of these methods attained the de-

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sired sensitivity and objectivity.

Scanning laser polarimeter (Nerve Fiber Analyzer I–NFA–I; Laser Diagnostic Technologies Ltd, San Diego, CA) is one of the first clinical devices for quantitative assessment of the retinal NFL thickness in the living human eye. It measures the retardation caused by the specific arrangement of the microtubules of the retinal ganglion cells. When a polarized light beam passes through the microtubules in the retinal NFL, the light is shifted and the amount of phase shift is called retardation; it correlates linearly with the thickness of the retinal NFL (4, 5). Each degree of retardation corresponded with a NFL thickness of approximately 7.4 µm in two enucleated monkey eyes (4).

Weinreb et al found significant differences in retardation between normal and glaucomatous eyes in the superior and inferior arcuate regions in their first studies with this instrument (6). The scanning laser polarimeter appears to provide reproducible measurements especially when they are taken by the same operator (7-9). The specificity and sensitivity for the detection of glaucoma are reported to be 93% and 96% respectively with NFA-I (10). Choplin at al, using the latest version of the instrument, NFA-GDx, suggested there was a clear demarcation between normal subjects and glaucoma patients with no overlap between the 95% confidence intervals using some parameters like the superior maxima (11). The NFA has been proposed for glaucoma screening studies (10, 11).

The present study was designed to establish whether the NFA-I could differentiate between glaucoma patients and patients suspected of having glaucoma on the basis of the disc appearance (without any visual field defects), and normal eyes.

METHODS

Polarimetric measurements were obtained from patients with glaucoma, from glaucoma suspects, and from healthy volunteers. Glaucoma cases were selected from the patients followed in our glaucoma clinic who met the following inclusion criteria: 1) intraocular pressure (IOP) 22 mmHg or more; 2) best corrected visual acuity 20/50 or better; 3) typical visual field defects as defined by three adjacent points down by 5-dB with one of the points down by at least 10dB, or two adjacent points down by 10-dB or a 10-dB difference across the nasal horizontal meridian in two adjacent points; 4) optic nerve head changes such as increased C/D>0.4, C/D asymmetry ≥ 0.2 (in early glaucoma cases with no specific visual field defects, glaucomatous optic nerve appearance combined with elevated IOP and moderate to severe glaucomatous visual field defects in the fellow eye led to the diagnosis of glaucoma).

Patients with suspect disc appearance (cup–to– disc–ratio >0.4 or an asymmetry of ≥ 0.2) detected during routine ophthalmologic examination with normal visual fields (without defects described above), IOP less than 22 mmHg, no family history of glaucoma and best corrected visual acuity 20/50 or better were included in suspected glaucoma group.

Visual field testing was done using the full-threshold 32 examination of the Octopus Perimeter. Only visual fields meeting the reliability criteria (false positive and false negative responses and fixation losses < 20%) were used for the assessments.

Age-matched control groups were extracted randomly from our normative database, comprising randomly selected single eyes of 180 healthy volunteers aging between 7 and 83 years (unpublished data). The healthy group included hospital personnel, students in the medical faculty and volunteers who attended the outpatient clinic for correction of refractive errors or for minor problems. Inclusion criteria included no family history of glaucoma, best corrected visual acuity 20/25 or better, IOP < 22 mmHg, C/D ratio <0.4, and no history of ocular disease except for refractive errors (±1.00 D or less) and minor problems like minimal blepharitis and allergic conjunctivitis.

Eighty eyes of 55 patients with glaucoma and 53 eyes of 30 patients suspected of glaucoma based on disc appearance met the inclusion criteria. Characteristics of the study groups are summarized in Table I. There was a significant difference between the mean ages of the study groups (Student's t test, p=0.0004),

TABLE I - MAIN CHARACTERISTICS OF THE STUDY GROUPS

Groups	Number of eyes	Age (years)	C/D Ratio
Glaucoma	80	53 ± 13	0.55 ± 0.22
Glaucoma suspect	53	45 ± 14	0.63 ± 0.14

so we formed separate age-matched control groups for each. The glaucoma group comprised 37 eyes with primary open angle glaucoma, 21 with normal tension glaucoma, 17 with pseudoexfoliative glaucoma, 3 with angle closure glaucoma, and 2 with juvenile glaucoma (most of them with moderate glacuomatous optic nerve damage).

Informed consent was obtained from subjects meeting the inclusion criteria and retinal NFL thickness was measured with the scanning laser polarimeter (NFA-I) which uses a light source consisting of a near infrared diode laser (wavelength 780 nm). The field of view is 15° and a complete scan consists of 65,536 individual retinal locations (256x256 pixels). The acquisition time is 0.7 seconds. A computer algorithm calculates the amount of retardation at each retinal position. Retardation was measured within a 10-pixel-wide band located concentrically with the disc margin at 1.75 disc diameters. The optic disc margin was approximated by a circle or ellipse placed around the inner margin of the peripapillary scleral ring. Mean absolute retardation was calculated for the superior (120°), inferior (120°), and nasal (50°) regions. We used the ratios to increase the precision of the instrument (because the NFA-I does not supply an absolute calibration), obtained by dividing the superior and inferior values by the nasal value, as suggested by Tjon-Fo-Sang et al (9). At least four good quality images were obtained for each patient and the best was selected for measurement. Our criteria for a good image were sharp focus, centrally located optic disc and equal illuminaton in all segments of the image. All the NFL measurements were done by the same experienced operator (S.C.Ö) to avoid inter-individual variability.

Student's t-test was used to compare the NFL ratios of age-matched control groups, glaucoma patients and glaucoma suspects. Linear regression analysis was applied to determine the relation between the NFL ratio and the C/D ratio in both groups and the mean defect (MD) in the glaucoma group.

RESULTS

NFL data for all groups are listed in Table II as the means and standard deviations for the three ratios. Although the glaucoma group had significantly lower NFL ratios than the control group there was ample overlap (Fig. 1). The superior and inferior NFL ratios in the suspected glaucoma group were also significantly lower than the control group, with even more overlapping (Fig. 2). Although statistically insignificant and not matched for age, the glaucoma group had lower NFL ratios than the glaucoma suspects (Student's t–test, p>0.05).

The average MD in glaucoma patients was 5.6 ± 3.1 (range 2.0-19.6). We also found that the superior and inferior NFL ratios in glaucoma patients gradually decreased as the MD in visual field increased. Linear regression analysis of all 80 superior NFL ratios (Fig. 3a)

TABLE II - NERVE FIBER LAYER DATA

	Glaucoma (±SD)	**Glaucoma control (±SD)**	**Glaucoma suspect (GS) (±SD)**	**GS-Control (±SD)**
S/N	2.34 ± 0.47	2.88 ± 0.48	2.63 ± 0.58	3.02 ± 0.64
	(1.50 - 3.60)	(1.54 - 4.16)	(1.43 - 3.79)	(1.89 - 4.57)
t-test	(t=–6.48, p=0.00)*		(t=–3.27, p=0.001)*	
I/N	2.46 ± 0.52	2.88 ± 0.48	2.73 ± 0.57	2.99 ± 0.49
	(1.41 - 3.89)	(1.70 - 3.89)	(1.35 - 3.88)	(1.75 - 4.03)
t-test	(t=–5.12, p=0.00)*		(t=–2.24, p=0.028)*	
S/I	0.94 ± 0.18	1.00 ± 0.13	0.96 ± 0.12	1.01 ± 0.16
	(0.62 - 1.33)	(0.72 - 1.36)	(0.68 - 1.31)	(0.78 - 1.52)
t-test	(t=–2.11, p=0.047)**		(t=–1.73, p=0.088)	

* Significant difference using Student's t-test

** After Bonferroni correction p=0.104, i.e. not significant

S/N: Superior/nasal, I/N: Inferior/nasal, S/I: Superior/inferior

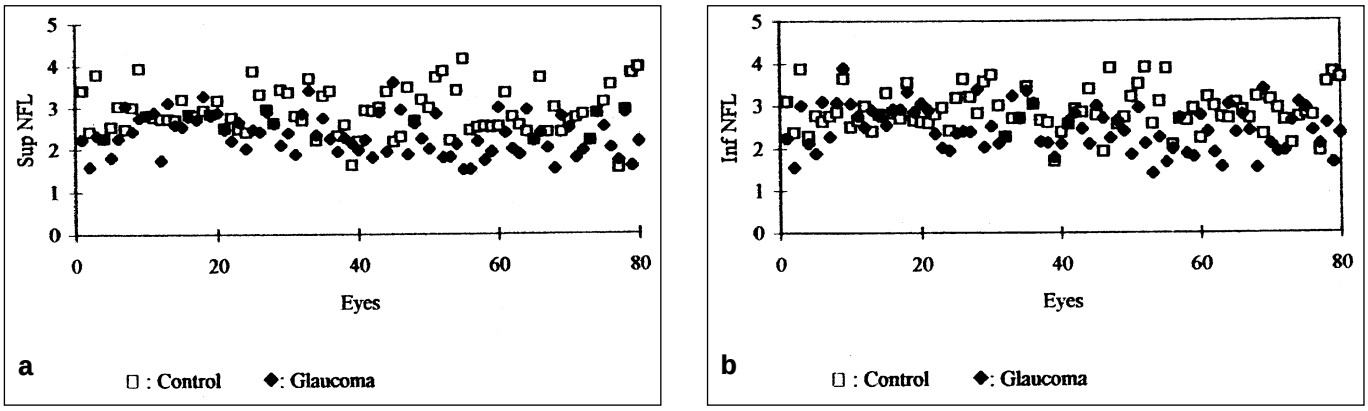

Fig. 1 - ***a.*** *Superior, and* ***b.*** *Inferior, NFL ratios of glaucomatous eyes and their control group.*

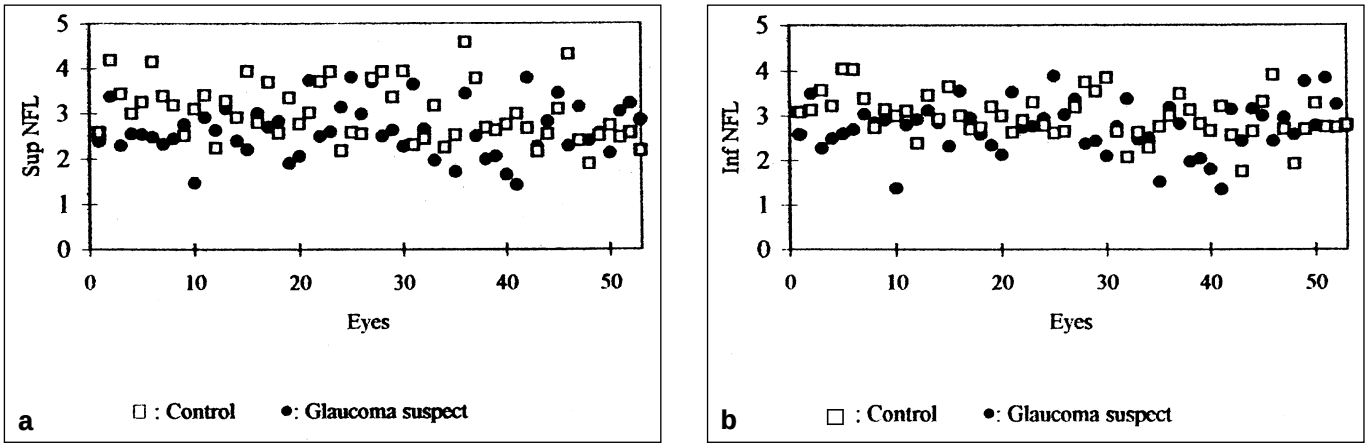

Fig. 2 - ***a.*** *Superior, and* ***b.*** *Inferior, NFL ratios of eyes suspected of glaucoma and their control group.*

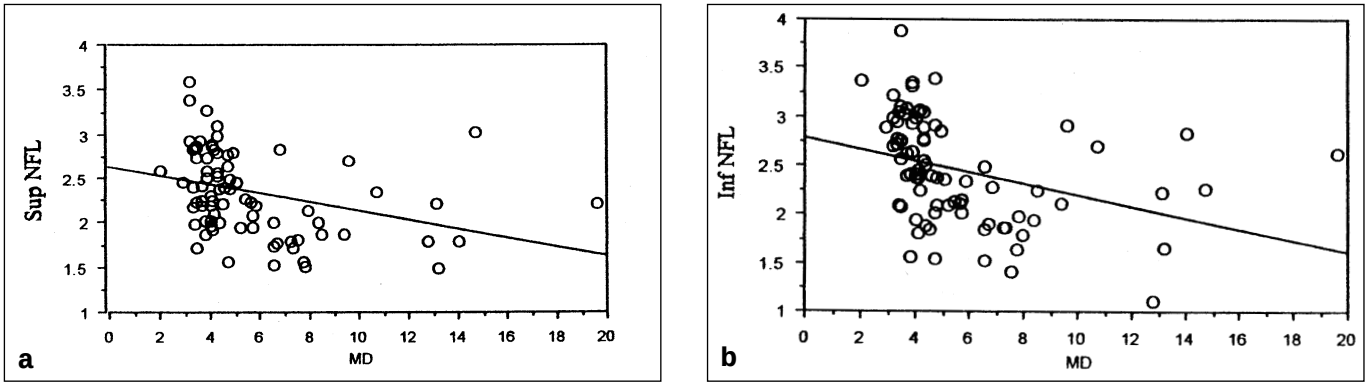

Fig. 3 - ***a.*** *Regression analysis of superior NFL ratios in glaucomatous eyes yielded a gradual, significant decline with MD (C.C –0.33, p=0.0025).* ***b.*** *Regression analysis of the inferior NFL ratios in glaucomatous eyes yielded a similar decline with MD (C.C. –0.34, p=0.0021).*

yielded a gradual and significant decline with MD (correlation coefficient [C.C.] –0.33, p=0.0025). Regression analysis of the inferior NFL ratios (Fig. 3b) yielded a similar decline with MD (C.C –0.34, p=0.0021). There was no change in the superior-to-inferior ratio with MD. Regression analysis of NFL ratios in glaucoma and suspected glaucoma patients did not show any significant change with C/D ratios.

DISCUSSION

Previous studies on glacoma patients have shown significant NFL loss using the scanning laser polarimeter (6, 10, 11). In one of the first studies on glaucoma patients by Weinreb et al, there was a mean retardation difference of about 13% between glaucomatous and normal eyes, with ample overlapping (6). Tjon-Fo-Sang et al reported that the superior or inferior NFL in patients with glaucoma was about 30% lower than in normals (10). In the present study, glaucomatous eyes had about 19% and 15% lower NFL ratios than the control groups for the superior and inferior regions, respectively.

Differences between these studies may be due to patient's characteristics (such as severity of glaucoma) and the exclusion or inclusion of highly variable areas with blood vessels, or to differences in the location of scanning laser polarimetry measurements. In the present study we did not exclude the highly variable areas with blood vessels, and the glaucoma in our patients was moderate (MD 5.6 on average). In the study by Tjon-Fo-Sang et al. MD was –10.27 on average (more severe glaucoma cases), and they excluded the areas with blood vessels, all of which had contributed to the increased sensitivity and specificity.

Although there was a significant difference between the glaucomatous eyes and the control group the values largely overlapped. The reason seems to be the wide variability of NFL thickness even among normal healthy subjects of the same age group (12) which made screening based on NFL measurements difficult. This normal variability in NFL thickness may be the result of individual differences in prenatal regression of retinal ganglion cells (13).

Glaucoma researchers have now concentrated on the detection of early glacuoma cases and distinguishing them correctly from normals and glaucoma suspects. This important topic is prospectively studied so as to start the appropriate treatment in early glaucoma patients before irreversible ganglion cell damage has taken place, and to avoid unnecessarily close follow-up with repeated visual field testing of healthy glaucoma suspects and normal people. Patients with ocular hypertension had significantly lower NFL thickness than normals, measured with the scanning laser polarimeter (11, 12, 14). Studies of patients suspected of having glaucoma on the basis of the disc appearance evidenced some NFL loss in these patients, using photography (15, 16).

The present study found that glaucoma suspects had NFL ratios respectively 13% and 8.5% less than the control group in the superior and inferior regions. Choplin et al raised a question about these patients: have they lost fibers from the superior bundle (like "low-tension" glaucoma) or are their nerve fiber layers anatomically different from normal (i.e., are the fibers distributed differently around the nerve head) (11)?

NFA-II was reported to differentiate between glaucomatous eyes, glacuoma suspects and normals without any overlapping within the 95% confidence intervals used (11). We found ample overlap between these patients and normals, as we had expected. Probably there were patients in this group, with early normal tension glaucoma who had not yet developed visual field defects, as well as healthy people, which resulted in a lower mean NFL than the control group.

Although the mean ages of the glacuoma (53y) and suspected glaucoma groups (45y) were different, meaning we cannot exclude an effect of age on NFL thickness, when we compared the two groups with respect to the mean NFL thickness, the glacuoma group had about a 10% less thick NFL than the suspected glaucoma group; this was not statistically significant and probably means that glaucoma suspects had a mean NFL ratio lower than normals but higher than in glaucomatous eyes.

We also found a moderate correlation between the NFL ratios and the MD in visual field in glaucoma patients, which is in agreement with previous studies (17-19). Regression analysis of C/D ratios in the patient groups, however, did not bring to light any significant correlation with the NFL ratios.

In conclusion, NFL ratios of glaucomatous eyes and eyes suspected of glaucoma based on disc appearance, measured with the NFA-I, were significantly low-

er than normal. NFA-I, however, is unable to differentiate between these patients and normals, at least with these parameters, because of the large area of overlap. NFA-I detected significant differences between normals and glaucoma suspects, so the instrument may possibly be an additional tool for glaucoma diagnosis. The overlap between the study groups, however, means that the NFA-I cannot replace any conventional diagnostic procedure so far. On the other hand, the NFA-I is now no longer on the market so this study serves to confirm the results of other studies with NFA-I and the newer versions NFA-II and GDx.

Our approach to patients suspected of glaucoma on the basis of disc appearance is to make a NFL assessment with the NFA and, if NFL ratios are lower, to follow them closely (three-monthly) with repeated examinations of visual fields (six-monthly), intraocular pressure and NFL (six-monthly). If their NFL values are normal we prefer to examine them at six monthly or yearly intervals.

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