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Retinal nerve fiber layer measurements using laser scanning polarimetry in different stages of glaucomatous optic nerve damage

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Abstract *Purpose:* To evaluate the diagnostic value of polarimetric measurements of the retinal nerve fiber layer (RNFL) thickness in different stages of glaucomatous optic nerve damage. *Methods:* The study included 92 eyes of 46 controls (age 41.0±13.7 years) and a heterogeneous group of 232 eyes of 135 patients with different stages of glaucomatous optic nerve damage (age 54.0±10.2 years; 68 patients with primary open-angle glaucoma, 56 with normal-pressure glaucoma and 11 patients with secondary glaucoma due to primary dispersion syndrome or pseudoexfoliation syndrome). All control subjects and patients underwent complete ophthalmological examinations including scanning laser polarimetry of the RNFL using the GDx (Laser Diagnostic Technologies, San Diego, Calif.) and 15° color stereo optic disc photographs. Only subjects and patients with disc area less than 3.4 mm^2 were included in the study. The total glaucoma group were divided into four subgroups according to the morphological criteria of the neuroretinal rim. *Results:* The stage of morphological glaucomatous optic nerve damage was classified as follows: stage 0: n=92, stage 1: n=103, stage 2: n=65, stage 3: n=40, and stage 4: n=19. Differences in mean polarimetric retardation between controls and eyes with glaucoma were significant for all parameters except the variable symmetry. The most significant differences between controls and eyes with glaucomatous optic nerve damage were found with the "number" variable assigned by the neural network analysis (P<0.001). With increasing stage of glaucomatous optic nerve damage, separation of the variable "the number" increased significantly. At a predetermined specificity of 90% the sensitivity of the groups with different stages of morphological glaucomatous optic nerve damage increased from 32% for stage 1 to 90% for stage 4. *Conclusion:* Polarimetric measurement of the RNFL thickness is significantly associated with morphological glaucomatous optic nerve damage. The fast performance, easy handling, and low cost of RNFL polarimetry mean that it can be included in the routine examination of glaucoma patients. Further study and refinement of this technique are indicated to improve its usefulness in both clinical diagnosis and in population-based case identification.

Introduction

The morphological examination of the optic nerve and evaluation of the retinal nerve fibers play an important role in diagnosis of glaucoma and other optic nerve diseases. Diagnostic modalities have so far been ophthalmoscopy [36], photography of the optic disc and retinal nerve fiber layer [1, 2, 14, 15, 18], confocal scanning laser tomography [5, 6, 21, 25] or scanning laser polarimetry [3, 7, 31, 32, 38, 39]. The latest method was reported to have potential value in the detection and follow-up in glaucoma because it provides an objective and fast measurement of the retinal nerve fiber layer (RNFL) thickness with good reproducibility of measurements. The purpose of this study was to ascertain the diagnostic value of polarimetric measurements of the RNFL thickness in different stages of glaucomatous optic nerve damage.

Subjects and methods

The study included a heterogeneous group of 232 eyes of 135 patients (age 54.0±10.2 years) with different stages of glaucomatous optic nerve damage and 92 normal eyes of 46 subjects (age 41.0±13.7 years). Exclusion criteria were all eye diseases other than glaucoma, diabetes mellitus, and a myopic refractive error exceeding –8 diopters. To avoid influence of the optic nerve size on the diagnostic value of scanning laser polarimetry for measurement of the thickness of the RNFL only subjects and patients with disc area less than 3.4 mm^2 were included in the study [13].

The normal subjects, recruited from the university administration staff and healthy attendants of the patients, were examined as control group. They did not show any abnormalities in the ophthalmological evaluation, which included slit-lamp examination, tonometry, visual field testing, gonioscopy, and ophthalmoscopy. Normal subjects showed a normal configuration of the neuroretinal rim in a disc with physiological cupping, with a typical pattern:

- Stage 0: the rim with is largest in the inferior optic disc region, followed by the superior, nasal, and temporal regions [16].

The patients' group was divided into three subgroups: 68 patients with primary open-angle glaucoma, characterized by intraocular pressure higher than 21 mmHg without any apparent reason; 11 patients with secondary open-angle glaucoma with elevated intraocular pressure measurements due to primary melanin dispersion syndrome (pigmentary glaucoma) or pseudoexfoliation of the lens (pseudoexfoliative glaucoma); and 56 patients with normal-pressure glaucoma. For the diagnosis of normal-pressure glaucoma, all intraocular pressure measurements obtained in at least two day-and-night intraocular pressure profiles had to be less than 21 mmHg without medication. Ophthalmoscopy, medical history, and neuroradiological, neurological, and medical examinations did not reveal any other reason than glaucoma for the optic nerve damage.

For all patients and controls, a 15° color stereo optic disc photograph had been taken using a telecentric fundus camera. The disc slides were projected in a scale of 1 to 15. The outlines of the optic cup, optic disc, peripapillary scleral ring and alpha and beta zones of parapapillary atrophy were plotted on paper and morphometrically analyzed. The photographs were evaluated in a masked fashion without knowledge of the clinical diagnosis and the visual field data. The method of the optic disc morphometry, the definition of the intra- and parapapillary structure and the correction of photographic magnification have been described in detail [16, 17]. Based on intrapapillary morphological criteria the total glaucoma group was divided into four stages [17, 19]:

- Stage 1: loss of normal configuration of the neuroretinal rim but no apparent notch in the neuroretinal rim
- Stage 2: notching of the neuroretinal rim in the lower temporal and/or upper temporal sector
- Stage 3: advanced glaucomatous cupping with extensive narrowing of the neuroretinal rim at the temporal border (focal notches no longer distinguishable)
- Stage 4: far advanced glaucomatous cupping with total loss of planimetrically neuroretinal rim at the temporal optic disc border

None of our patient showed glaucomatous optic nerve damage of stage 5, with total loss of all neuroretinal rim (absolute glaucoma).

All patients and subjects included in the study underwent scanning laser polarimetric examination of the RNFL using the nerve fiber analyzer GDx (Laser Diagnostic Technologies, San Diego, California; software package 2.09). Detailed descriptions of the GDx have been published previously [3, 31, 32, 38]. Briefly, a beam of polarized laser light is sent to the birefringent RNFL and is partially reflected from the deeper layers of the retina. By an integrated polarimeter, the device measures the change of polarization of incident light as it doubly passes through the RNFL. This process is also known as retardation. The light source is a 780-nm diode laser in which the state of polarization is modulated. The light emerging from the eye and collected by the instrument is separated from the illuminating light beam by a non-polarizing beam splitter. Consequently, the polarization state of the light is analyzed by the polarimeter. Images with an overall quality score of less than 95% (about 4% of all patients) were not included in the study. The examination was performed under photopic conditions without requiring dilatation of the pupil. The peripapillary region was divided into a superior sector and an inferior sector each measuring 120°, a temporal sector of 50°, and a nasal sector of 70°. The off-line evaluation of the images and the definition of the measurement ellipse were made by two skilled examiners. The following GDx variables were collected and included in statistical analyses: symmetry, superior ratio, inferior ratio, superior to nasal ratio, average thickness, maximum modulation, ellipse modulation, ellipse average, superior average, inferior average, and "the number". The meaning of each parameter has been previously reported in details [24, 38]. All variables were automatically calculated using GDx software based on a large GDx normative database. For "the number", a trained neural network assesses all pixels and assigns a number ranging from 0 (completely normal) to 100 (advanced glaucoma) to every eye tested. Symmetry is the ratio of the average of 1,500 thickest pixels in the superior quadrant tothe average of 1,500 thickest pixels in the inferior quadrant. Four ratios of thickness values were given: the ratio of the average of the 1,500 thickest pixels in the superior quadrant to the 1,500 thickest pixels in the inferior quadrant and analogously, the ratios of the average of the 1,500 thickest pixels in the superior or inferior region to the 1,500 median pixels in the temporal or nasal quadrant. The maximal modulation of the areas and the modulation of the ellipse were indications of regional differences between the thickest and thinnest part of the nerve fiber layer. The average thickness of the pixels of an image was given for all usable pixels outside the ellipse, for all pixels on the entire ellipse, and for pixels on the superior and inferior part of the ellipse.

All subjects and patients were consecutively examined. The study followed the tenets of the Declaration of Helsinki for research involving human subjects and informed consent was obtained from all participants of the study.

If both eyes had been examined, only one randomly chosen eye per patient was taken for statistical analysis.

Table 1 Clinical data of controls and patients with different stages of glaucomatous optic nerve damage

	Controls	Glaucomatous optic nerve			
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Number of eyes	92	103	65	40	19
Number of patients	46	57	41	22	15
Age (years)	41.0±13.7	52.1±9.6	53.9±11.0	56.4±11.0	56.6±8.4
Refractive error (D)	–1.4±2.1	–1.2±2.1	–2.1±3.1	–1.5±2.9	–1.4±2.1
Visual field defect (MD)	0.7±1.2	1.7±1.7	5.5±4.1	9.5±5.5	11.3±5.6
Maximal previous IOD (mmHg)	18.1±3.8	26.8±7.1	26.6±8.1	26.0±7.8	25.0±8.4
IOD on examination day (mmHg)	15.6±2.8	18.1±3.9	16.4±3.2	17.5±3.8	16.4±3.2

Table 2 Mean values and standard deviation of all raw data delivered by the nerve fiber layer polarimeter. *Asterisks* indicate significant results of Mann Whitney tests

Parameter	Controls	Glaucomatous optic nerve			
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
"The number"	16.9±9.7	26.5±17.5***	44.6±25.7***	51.5±24.5***	58.7±22.3***
Superior ratio	2.27±0.4	2.04±0.4**	1.79±0.5***	1.69±0.3***	1.48±0.2***
Inferior ratio	2.41±0.4	2.14±0.4**	1.86±0.4***	1.77±0.3***	1.61±0.3***
Superior/nasal	2.05±0.3	1.89±0.3*	1.72±0.4***	1.56±0.3***	1.37±0.2***
Max. modulation	1.54±0.4	1.27±0.4**	1.10±0.4***	0.88±0.3***	0.69±0.3***
Ellipse modulation	2.59±0.7	2.25±0.6*	2.09±0.6**	1.72±0.5***	1.28±0.3***
Average thickness	66.0±13.8	61.8±11.7	59.5±9.3*	58.8±11.9*	60.8±13.1*
Ellipse average	70.1±14.0	64.9±11.9**	57.8±9.9***	59.0±13.1***	61.1±13.5***
Superior average	77.1±16.0	70.0±13.8*	60.7±13.2***	61.8±15.2***	61.8±15.5***
Inferior average	84.1±17.4	76.6±16.1*	66.5±14.4***	66.6±15.2***	67.7±15.6***
Symmetry	0.95±0.1	0.96±0.1	0.97±0.2	0.97±0.2	0.96±0.2

*P<0.05, not significant after Bonferroni correction
**P<0.01, significant after Bonferroni correction
***P<0.001, significant after Bonferroni correction

The data were processed using a personal computer and statistically analyzed using SPSS 10.0 for Windows NT. Measurement values of variables of different stages were described with mean and standard deviation. Comparisons between groups were made using the Mann–Whitney test (U-test). For tests of significance the "raw" results without any correction for multiple testing were given as well as Bonferroni-corrected results. The Bonferroni correction is performed by multiplying the observed P value by the number of tests performed. In our study, with 5 subgroups and 11 variables, this number was 55. Sensitivity and specificity were used to describe the diagnostic value of the procedures [4].

Results

The stage of morphological glaucomatous optic nerve damage was classified as follows: stage 0: n=92, stage 1: n=103; stage 2: n=65, stage 3: n=40 and stage 4: n=19. The age, intraocular pressure (IOP) on examination day or maximal previous IOP, and visual field mean deviation (MD) in control subjects and patients with different stages of morphological glaucoma optic nerve damage are listed in Table 1. After Bonferroni correction, except for symmetry, average thickness, ellipse average, superior average, and inferior average, all parameters differed significantly between controls and eyes with stage 1 of morphological glaucoma optic nerve damage. The more advanced the glaucomatous optic nerve damage, the more significantly differed the means of the measured variables between the study groups (Table 2). The most significant differences between controls and eyes with glaucomatous optic nerve damage were found with the "number" variable assigned by the neural network analysis (P<0.001 after Bonferroni correction).With advancing stage of glaucomatous optic nerve damage, separation of the variable "the number" increased significantly (Fig. 1). Sensitivities calculated at a specificity of 90% were relatively low for symmetry, average thickness, ellipse average, superior average, and inferior average (Table 3). Sensitivities were higher for the variables superior ratio, inferior ratio, superior to nasal ratio, maximum modulation, and ellipse modulation and it was highest for "the number". At a predetermined specificity of 90% the sensitivity of the group with different stage of morphological glaucomatous optic nerve damage increased from 32% for stage 1 to 90% for stage 4 (Table 3).

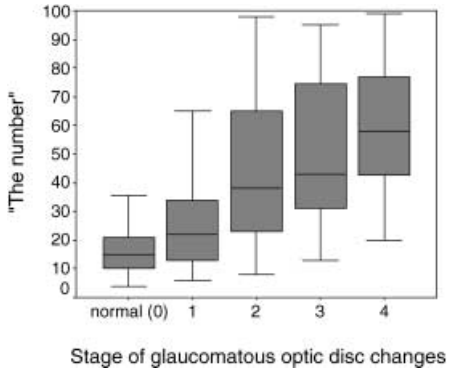

Fig. 1 Boxplots of variable "the number" delivered by the nerve fiber layer polarimeter in controls and four glaucomatous subgroups. The *boxes* include 50% of the measured values (between the 25th and 75th percentiles) and show the position of the median (*horizontal line*). The *error bars* indicate 1.5 times the interquartile distance from the upper and lower box edge

Table 3 Sensitivities (%) of the nerve fiber layer polarimetric measurements to separate patients of the glaucoma group with different stages of glaucomatous optic nerve damage from the subjects of the normal control group. Values are calculated for a specificity of 90%

Parameter	Stage 1	Stage 2	Stage 3	Stage 4
"The number"	32	65	83	90
Superior ratio	20	44	60	88
Inferior ratio	23	48	63	78
Superior/nasal	20	45	65	84
Max. modulation	26	46	75	84
Ellipse modulation	19	26	60	79
Average thickness	14	23	28	32
Ellipse average	21	44	45	47
Superior average	20	42	40	45
Inferior average	19	43	48	46
Symmetry	10	10	10	15

Discussion

Traditionally glaucoma has been defined by the triad of increased intraocular pressure, optic disc changes, and visual field defects. Histological studies have shown, however, that there may be a significant loss of ganglion cells before evidence of functional loss on conventional visual field testing [25]. Previous studies have shown an association between functional properties and structural alteration of the RNFL [22, 33, 37] and that certain changes in optic nerve disc structure and a localized or diffuse loss of RNFL thickness may precede visual field defects [8, 26, 29]. To prevent damage, it is important to detect glaucomatous RNFL changes as early as possible in order to find an efficient treatment for glaucoma. Therefore evaluation of RNFL thinning is not only for detecting but also for monitoring glaucoma. The RNFL can be visualized and evaluated by routine ophthalmoscopy using green light [36], by taking black-and-white wide-angle fundus photographs using blue light [2, 14, 15, 18, 29], by confocal scanning laser tomography of the optic nerve head [6, 37], and by optical coherence tomography [28]. The diagnosis of the RNFL using photography has been established as a standard method in glaucoma patients [1, 14,34]. However, evaluation of RNFL photography is usually qualitative and subjective and depends on the examiner's experience. Scanning laser polarimetry (SLP) is a new non-invasive diagnostic technique for assessment of the nerve fiber layer thickness in the parapapillary retina. This method provides quantitative and objective information, and the measurements are acquired rapidly and often do not require pupil dilation [27, 30, 31, 32, 33, 39, 40, 41, 42]. Kremmer et al. found in a comparative study that SLP and fundus photography showed good agreement with regard to grading of retinal fiber layer damage; however, SLP had advantages over fundus photography because of a higher rate of good-quality images and quantitative measurements [20]. In our patient groups about 4% of the laser polarimetric scans had quality score less than 95% and was therefore excluded from the study; this finding is in accordance with the results of Kremmer et al. [20]. In the present study, RNFL retardation measurements obtained with the SLP were significant altered in eyes with glaucomatous optic disc damage compared with normal eyes. The more advanced the morphological optic nerve damage, the more significantly differed the means of the measured variables between normal eyes and eyes with glaucoma. The findings indicate that RNFL thickness measured by SLP correlates well with different stages of morphological optic nerve changes and that measurement with SLP reflects the severity of glaucomatous optic nerve damage. Although most patients with optic nerve damage of stage 1, as indicated by RNFL measured by SLP, do not have visual field loss, especially, "the number" is already significantly altered (Table 2). The results of the present study suggest that SLP is able to unmask a considerable proportion of glaucoma patients with morphological signs of optic disc damage before the achromatic visual field examinations become pathological. However, at a predetermined specificity of 90% the sensitivity of the group with morphological glaucomatous optic nerve damage stage 1 is not very high (32%). A combination of SLP and papillometry may improve the ability to discriminate between normal eyes and glaucoma eyes in the early stage. The sensitivity of SLP increased significantly up to 90% in patients with advanced glaucomatous optic nerve damage (Table 3). Our findings may contrast with the high sensitivity and specificity described by Tjon-Fo-Sang and Lemij [29] but they coincide with many results reported by other authors [12, 24, 39]. The subgroup of stage 4 in our study is small (19 eyes); only 2 eyes of two patients with low tension glaucoma (10%) could not separated directly

through the variable “the number” from the normal groups. However the values of their “number” were at the upper limit.

Previous studies showed a statistically significant correlation between the polarimetric data and the mean perimetric defect or the neuroretinal rim area in glaucoma patients [7, 12, 24]. In the present study we showed that RNFL thickness as measured by means of polarimetry is significantly associated with morphological stages of glaucomatous optic nerve damages.

The symmetry parameter was the only one that was not different between normal and glaucoma at any stage. This finding confirms the previous observation of another study [24, 37, 38] that stressed the large range of normal mean values of retardation. Recent investigations have revealed that a multivariate analysis including several optic disc variables increases sensitivity and specificity of the morphological assessment of the optic nerve head in the detection of glaucomatous optic nerve damage [5, 23, 35]; the present study showed a similar result for the polarimetric evaluation of the RNFL. Of all measured variables, “the number”, which was derived from a neural network calculation, had the highest diagnostic power. However, there is an overlap between the normal eyes and eyes with early glaucomatous nerve damage in the range of values for all these parameters (Fig. 1). This overlap may be related to wide variations in RNFL among the healthy individuals. SLP evaluated the thickness of the RNFL by using the birefringent properties of nerve fiber. When polarized light makes a double pass through such birefringent tissue, its polarization state changes. The change in polarization of the scanning beam, the so-called retardation, is proportional to the thickness of the birefringent medium and is measured to give an index of RNFL thickness [31, 38]. Because the RNFL is not the only ocular birefringent structure, this technology incorporates a proprietary anterior segment compensator device to neutralize the polarization effects of the cornea and crystalline lens. The anterior segment compensator assumes all individuals to have a fixed slow axis of cornea birefringence, called the corneal polarization axis, of 15° nasally downward [10]. Recently, considerable intra- and interindividual corneal polarization axis variability has been described, and there is evidence that the corneal polarization axis strongly affects peripapillary retardation measurements [9, 10]. This observation may explain the wide distribution of normative RNFL thickness data in healthy individuals. Greenfield et al. found in their previous study that the anterior segment compensation device is not entirely capable of neutralizing the polarization properties of cornea that deviate from the axis [10]. Eyes that deviate widely are characterized by strong peripapillary retardation that artifactually increases the apparent RNFL thickness. In contrast, eyes with corneal polarization axis closer to the compensator axis are characterized by weaker peripapillary retardation resulting in lower measured RNFL thickness [9]. The relationship between corneal polarization axis and RNFL thickness determination may limit the discriminating power of SLP.

Potential error in the polarimetric measurements of the RNFL thickness relates to ocular factors which may alter the polarization of light, implicating the cornea and the lens. It also suggests that the validity of nerve fiber layer polarimetry may be increased if the interindividual variability in corneal light polarization can be taken into account. In a previous study Greenfield et al. evaluated the longitudinal stability of the corneal polarization axis on SLP measurements. They concluded that corneal polarization axis does not contribute significantly to longitudinal changes in RNFL thickness as assessed by SLP among eyes without pathological changes of the cornea [9]. There was a strong relation between RNFL thickness and deviation of the eyes from the compensation axis. Eyes with corneal polarization axis closer to (18°) or farther from (76°) the compensator axis have RNFL thickness measurements that exceed the 95% confidence intervals for normals [9].

It is important to know other causes of variability in retardation images. Poor image quality and poor reproducibility have been reported in eyes with corneal grafts or edema, keratic precipitates, anterior uveitis, lenticular or vitreous opacity, posterior staphyloma, and high-axis myopia [11]. Care must be taken in performance and assessment of SLP to maximize measurement quality and reproducibility.

Although this study is only a cross section, the fact that polarimetric RNFL thickness correlates well with different stages of morphological glaucomatous optic nerve damage suggests that this method may be useful for follow-up of glaucoma suspects and patients. Longitudinal studies are necessary to address this question.

In conclusion, scanning laser polarimetry of the retinal nerve fiber layer is an additional tool for glaucoma diagnosis; it reflects the severity of glaucomatous optic nerve damage. Because of its easy handling, the short examination time (less than 5 min per patient), the low running costs and low cost of each examination, and its relatively high reliability this method may be incorporated into the routine examination of glaucoma patients. Further study and refinement of this technique are indicated to improve its usefulness both in clinical diagnosis and in population-based case identification.

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