Influence of atypical retardation pattern on the peripapillary retinal nerve fibre distribution assessed by scanning laser polarimetry and optical coherence tomography

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ABSTRACT

Aim To investigate the influence of atypical retardation pattern (ARP) on the distribution of peripapillary retinal nerve fibre layer (RNFL) thickness measured with scanning laser polarimetry in healthy individuals and to compare these results with RNFL thickness from spectral domain optical coherence tomography (OCT) in the same subjects.

Methods 120 healthy subjects were investigated in this study. All volunteers received detailed ophthalmological examination, GDx variable corneal compensation (VCC) and Spectralis-OCT. The subjects were divided into four subgroups according to their typical scan score (TSS): very typical with $TSS=100$, typical with $99 \geq TSS \geq 91$, less typical with $90 \geq TSS \geq 81$ and atypical with $TSS \leq 80$. Deviations from very typical normal values were calculated for 32 sectors for each group.

Results There was a systematic variation of the RNFL thickness deviation around the optic nerve head in the atypical group for the GDxVCC results. The highest percentage deviation of about 96% appeared temporal with decreasing deviation towards the superior and inferior sectors, and nasal sectors exhibited a deviation of 30%. Percentage deviations from very typical RNFL values decreased with increasing TSS. No systematic variation could be found if the RNFL thickness deviation between different TSS-groups was compared with the OCT results.

Conclusions The ARP has a major impact on the peripapillary RNFL distribution assessed by GDx VCC; thus, the TSS should be included in the standard printout.

INTRODUCTION

Scanning laser polarimetry (SLP) has become a widely used non-invasive imaging technique to quantitatively evaluate the peripapillary retinal nerve fibre layer thickness (RNFL) as part of a glaucoma workup. SLP uses the polarisation properties of light to determine the phase retardation induced by the birefringent microtubules within the RNFL. By conversion of RNFL-induced phase retardation using a fixed conversion factor, RNFL thickness is estimated.¹

GDx variable corneal compensation (VCC) is equipped with a variable corneal compensation and uses the macular birefringence pattern to neutralise for the corneal birefringence. SLP with VCC provides a more accurate measurement of RNFL compared with SLP with fixed compensation.²

However, a subset of eyes scanned by GDx VCC exhibit an 'atypical retardation pattern' (ARP) that produces artificial disturbances concerning measurement of RNFL thickness. To quantify the presence of ARP, GDx VCC provides the typical scan score (TSS). This value ranges from 0 (atypical) to 100 (very typical) and is based on a support vector machine.³ The TSS is not included on the standard printout of GDx VCC, but it is available via electronic data export.

Recent studies have shown that the diagnostic performance of RNFL thickness parameters is significantly reduced due to ARP.⁴

Predictors for ARP have been identified: an increased axial length and the presence of β para-papillary atrophy are associated with ARP for GDx VCC.⁵ The physical principles for development of ARP are not yet fully understood; however, using a polarisation sensitive optical coherence tomography (OCT), it has been shown that additional retardation of scleral origin contributes to development of ARP.⁶

Over the past two decades, OCT has become a rapidly evolving imaging technique that provides real-time, high-resolution images of tissues. OCT is the optical analogue of ultrasonic B mode imaging, but it utilises light instead of sound. Using the principles of low coherence interferometry,⁷ it acquires high-resolution images of ocular structure and allows cross-sectional in vivo imaging of retina and segmentation of intraretinal layers. The development from the original time-domain OCT (TD-OCT) to spectral-domain OCT (SD-OCT) increased acquisition speed up to 110-fold and axial resolution two- to threefold. However, glaucoma discrimination is comparable for TD-OCT and SD-OCT.⁸

The purpose of this study is to investigate the influence of ARP on the distribution of peripapillary RNFL thickness measured by scanning laser polarimetry in healthy individuals and to compare these results with RNFL thickness from spectral domain OCT in the same subjects.

METHODS

Subjects

The study was approved by our institutional review board and complied with the tenets of Declaration of Helsinki. One hundred and twenty normal subjects included in this study were recruited from the Erlangen Glaucoma Registry

Clinical science

(table 1). The Erlangen Glaucoma Registry is a clinical registry for cross-sectional and longitudinal observation study of patients with open angle glaucoma (OAG) or glaucoma suspect.⁹ Normal subjects were from the general population, as well as from the staff and employees of the University Erlangen-Nuremberg. All subjects underwent a standard ophthalmic examination including slit-lamp inspection, Goldmann tonometry, perimetry, funduscopy, gonioscopy and papillometry. Optic disc evaluations were based on 15° colour photographs (Zeiss telecentric fundus camera, Germany).

For inclusion in this study, subjects had to meet the following criteria: (1) completely normal findings in slit-lamp inspection; (2) intraocular pressure lower or equal 21 mm Hg; (3) normal optic disc; (4) best-corrected visual acuity of 20/25 or better; (5) normal and reliable visual field.

One randomly selected eye of each patient was used in this study.

Optic discs were evaluated using colour photographs and classified as normal by at least two experienced ophthalmologists. Criteria fulfilled the ISNT rule (which states that for normal optic discs, the neuroretinal rim width shows a characteristic configuration of inferior≥superior≥nasal≥temporal), good visibility of the peripapillary RNFL, absence of optic haemorrhages and no enlargement of the optic disc cup in relation to the optic disc size as well as absence of neuroretinal rim notching or thinning. Subjects were excluded if the refractive error exceeded a 5 D equivalent sphere or 2 D of astigmatism.

Perimetry

All subjects underwent visual-field tests with standard white-on-white perimetry with a computerised static projection perimeter (Octopus 500; Haag-Streit). All subjects had a normal visual-field test. The false-negative and -positive rate had to be lower than 12%. Criteria for pathological visual-field test were the presence of three adjacent test points with $p<0.05$ or two adjacent test points with $p<0.01$ in the pattern deviation map evaluated with Peridata software (Version 2.2.3).

Scanning laser polarimetry

Scanning laser polarimetry (SLP) was performed using GDx VCC. The images provided by GDx VCC were analysed with

software version 5.5.0. To ensure accurate corneal measurement, the software provides an image quality check score (1 to 10) based on the correct alignment, fixation and refraction of the scan. Only scans with a centred optic disc, a sharp and evenly illuminated reflectance image and an image quality scan score of 9 or 10 were accepted in the present study. However, all TSS values were included. The RNFL thickness measurements were obtained in an annulus around the optic disc (inner diameter 2.51 mm; outer diameter 3.26 mm). In order to evaluate the relationship between ARP and the distribution of peripapillary RNFL, the thickness values of 64 sectors and the typical scan score (TSS) were exported from the instrument. According to the TSS value, the subjects were divided into four groups: TSS=100, very typical retardation pattern; $99\geq TSS\geq 91$, typical retardation pattern; $90\geq TSS\geq 81$, less typical retardation pattern; and $TSS\leq 80$, atypical retardation pattern.

Optical coherence tomography

All subjects were scanned using a commercially available SD-OCT system (Spectralis HRA+OCT; Heidelberg Engineering, Germany). Infrared reflection images ($\lambda=820$ nm) and OCT B-scans ($\lambda=870$ nm, 40 000 A-scans/s) of the dual laser scanning systems are acquired simultaneously. Sixteen consecutive circular B-scans (3.4 mm diameter, 768 A-scans) centred at the optic disc were automatically averaged to reduce speckle noise. An online tracking system compensates for eye movements during data acquisition. An experienced operator (RPT) carefully controlled the scans for artefacts and segmentation failure. The 768 segmentation values of the inner limiting membrane and posterior RNFL boundary provided by the Spectralis software were exported, and the thickness distribution of peripapillary RNFL was calculated.

Calculation and statistical analyses

For both instruments, the exported peripapillary RNFL thickness values were averaged to 32 sectors (11.25° each) with the first sector corresponding to 9 o'clock (right eye) and the following sectors continuing clockwise according to the well-established convention. Measurements of left eyes have been mirror imaged before being analysed clockwise.

Table 1 Demographic and clinical differences of the subjects included

	Very typical	Typical	Less typical	Atypical	p Value*
No of subjects	40	41	22	17	
Typical scan score	100±0	95.4±3.0†	85.1±2.7†‡	60.3±16.7†‡	<0.001
Gender					
Female	14	14	6	4	0.821
Male	26	27	16	13	
Age (years)	47.3±13.7	50.9±12.7	52.5±13.3	53.6±16.7	0.235
Spherical refraction (mean D±SD)	-0.19±1.35	-0.45±1.8	-0.53±1.77	-0.90±1.72	0.641
Cylindrical refraction (mean D±SD)	0.20±0.36	0.37±0.63	0.63±1.1	0.37±0.68	0.146
Visual field MD (mean±SD)	-0.23±1.33	-0.48±0.92	-0.21±1.1	-0.24±0.92	0.863
Pattern SD (mean±SD)	1.61±0.37	1.46±0.52	1.61±0.46	1.53±0.37	0.664
Nerve fibre indicator (GDx VCC)	15.6±8.0	13.6±6.9	14.5±7.7	13.2±6.2	0.569
Temporal—superior—nasal— inferior—temporal mean (GDx VCC)	54.2±5.4	56.7±4.3	57.6±5.4	61.8±5.1†‡	<0.001
Retinal nerve fibre layer thickness (Spectralis optical coherence tomography, µm)	95.2±8.4	96.0±7.3	96.8±9.1	96.0±12.1	0.913

*Differences between groups were tested for statistical significance with ANOVA for continuous variables and with the Pearson χ^2 test for dichotomous variables.

†Indication of which mean is different from the very typical group (pairwise comparisons on the Tukey honestly significant difference test).

‡Indication of which mean is different from the typical group (pairwise comparisons on the Tukey honestly significant difference test). The typical scan score, age, refraction (ametropia), visual field mean deviation and pattern SD are presented as mean±SD.

To assess differences in RNFL thickness as determined with the GDx VCC and Spectralis OCT in 32 peripapillary sectors between subgroups, we used two-tailed *t* tests with respect to continuous variables with normal distribution based on histogram plots. Non-parametric (Mann–Whitney test) tests were used for continuous variables if data were non-normally distributed.

To evaluate demographic and clinical differences between subgroups, we used a one-way analysis of variance with post hoc Tukey honestly significant difference with respect to continuous variables (age, refraction, visual field mean deviation, pattern SD, nerve fibre indicator (NFI), temporal–superior–nasal–inferior–temporal (TSNIT) mean and RNFL thickness). For differences in dichotomous variables between groups, we used the Pearson χ^2 test. Associations of local RNFL values with TSS were evaluated using the Spearman correlation coefficient. A *p* value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 17.0.

RESULTS

Complete data and statistical results are presented in table 1. Forty of 120 healthy subjects (33.3%) imaged by GDx-VCC showed a TSS of 100, 41 subjects (34.2%) between 90 and 99, 22 subjects (18.3%) between 81 and 89, and 17 subjects (14.2%) below 81.

The TSNIT mean of GDx VCC increased significantly in the atypical group compared with the very typical and the typical group ($p<0.001$ and $p=0.006$). The RNFL thickness of the Spectralis OCT did not differ significantly between the groups.

Both imaging devices demonstrated a similar double-hump pattern in the RNFL profiles for all TSS subgroups with maximum RNFL thickness located at the superior and inferior sectors (figure 1).

The mean percentage deviation including 95% CI of the RNFL thickness around the ONH in three TSS groups compared with the group with TSS=100 measured by GDx VCC (A) and Spectralis OCT (B) is shown in figure 2. There was a systematic variation in RNFL thickness deviation around the ONH in the atypical group compared with the group with TSS=100 for the GDxVCC results. The highest percentage deviation of about 96% appeared in sector 1 (temporal) with decreasing deviation towards the superior and inferior sectors. A second relative maximum can be seen in the nasal sectors. Similar behaviour can be seen in the less typical and typical group. However, percentage deviations from very typical RNFL thickness decreased with increasing TSS.

TSS correlated inversely with age ($r=-0.244$, $p=0.007$), whereas refractive error, the nerve fibre indicator (NFI) and the RNFL thickness of the peripapillary sectors as determined by Spectralis OCT did not (table 2).

DISCUSSION

In this study, we compared peripapillary RNFL thickness results from SLP with SD-OCT results in the same subjects in a healthy study population. Our assumption was that the SD-OCT RNFL thickness results are more reliable compared with SLP results and can be taken as reference data. SD-OCT can also be affected by artefacts—for example, segmentation algorithm failure. However, B-scan images have been visually controlled for

Figure 1 Mean retinal nerve fibre layer (RNFL) thickness as determined with the GDx variable corneal compensation (VCC) (A) and Spectralis optical coherence tomography (OCT) (B) in 32 peripapillary sectors around the optic nerve head for four different typical scan score (TSS) groups. Very typical: TSS=100; typical: $99 \geq \text{TSS} \geq 91$; less typical: $90 \geq \text{TSS} \geq 81$; and atypical: $\text{TSS} \leq 80$.

Figure 2 Mean percentage deviation of the retinal nerve fibre layer (RNFL) thickness around the optic nerve head in three typical scan score (TSS) groups compared with the group with TSS=100 measured by GDx variable corneal compensation (VCC) (A) and Spectralis optical coherence tomography (OCT) (B). The asterisk indicates the significant difference ($p < 0.05$) between the RNFL thickness around the optic nerve head for each TSS group compared with the group with TSS=100.

artefacts and segmentation failure in this study. In contrast, artefacts of the SLP results caused by the birefringent sclera cannot be uncovered by the user of the instrument.

To our knowledge, this study provides the first quantitative data with high angular resolution on the effect of ARP on peripapillary RNFL thickness. The results show that the ARP has a major impact on the peripapillary RNFL distribution assessed by GDx VCC and that these ARP are thickness errors of the SLP measurements and cannot be explained by nerve

fibre distribution. In accordance with the study by Qiu and coworkers,⁵ we found that TSS is inversely correlated with age. However, the effect of refractive error on ARP is uncertain. One study demonstrated a significantly higher prevalence of ARP in myopic eyes.¹⁰ Contrarily, two studies found no significant correlation between ARP and refractive error.^{3 11} The LALES study,¹² a large population-based, cross-sectional study, showed axial length, corneal power and nuclear opalescence to be strong determinants of refractive error for adult latinos. Thus, the influence of different parameters might explain the different results of the studies mentioned above. In our study, the refractive error of subjects included did not exceed 5 D.

Several studies found strong relationships between mean RNFL thickness measured by GDx VCC and standard automated perimetry in glaucomatous patients. However, this could not be proved for localised RNFL defects in the papillo-macular bundle. Horn and coworkers^{13 14} failed to show a significant correlation between temporal optic disc sector and the corresponding central visual field area, and demonstrated only a weak correlation between nasal optic disc sector and temporal visual field area. Some studies suggested that the new GDx Enhanced Corneal Compensation (ECC) technology might improve the structure–function relationship,^{15 16} but still failed to show a significant correlation for the temporal sector.

In normal subjects with low TSS, the GDx parameter NFI remains reasonably uninfluenced by the ARP. The reason for this could be that this index is calculated from approximately 200 parameters trained using a neural network. However, Bowd

Table 2 Association between typical scan score and refractive error, nerve fibre indicator and age and retinal nerve fibre layer (RNFL) thickness in eight peripapillary regions as determined by Spectralis optical coherence tomography (OCT)

	Correlation coefficient	p Value*
Refractive error	0.018	0.843
Nerve fibre indicator	0.050	0.585
Age	−0.244	0.007
Location of retinal nerve fibre layer thickness		
Supero-temporal	−0.068	0.456
Temporo-superior	−0.026	0.777
Naso-superior	0.037	0.689
Supero-nasal	0.039	0.667
Infero-nasal	−0.063	0.488
Naso-inferior	−0.039	0.670
Temporo-inferior	0.032	0.730
Infero-temporal	0.013	0.886

*Data are expressed as the Spearman rank correlation coefficient. RNFL thickness data were measured by Spectralis OCT in healthy eyes.

*et al*¹⁷ showed that for glaucoma patients with a low TSS, the diagnostic accuracy of the NFI decreases, and thus glaucoma patients exhibiting ARP are prone to be classified false negative by the NFI.

RNFL thickness measurements of GDx VCC scans with TSS <80 have to be evaluated with caution, as expected earlier.¹⁷ Consequently, in our opinion, TSS should be included in the standard printout of the GDx VCC.

According to the effect that the deviation of RNFL thickness is highest where the RNFL thickness is low (and vice versa), our study supports the hypothesis that additional retardation of scleral origin causes ARP, possibly due to increased penetration of the probing beam of SLP.⁶ Nasal and temporal sectors around the optic disc might be especially susceptible for increased penetration into the sclera, since the RNFL thickness is lower in those sectors than in the superior and inferior sectors. In other words, a high RNFL thickness protects the SLP measurements from unwanted light reflected back from the birefringent sclera and also improves the signal-to-noise ratio. SLP images used in the presented study were controlled for excessive parapapillary atrophy, which may interfere with the measurement.

Recent studies reported on a lower prevalence of ARP with GDx ECC compared with GDx VCC.^{5 10 18} ECC is a new software method for increasing the signal-to-noise ratio in areas of low signal.¹⁹

In the ECC mode, the compensator is adjusted so that it combines with the corneal retardation to produce a bias retardation of approximately 55 nm into the signal path with the slow axis close to vertical. The SLP measures a higher total retardation than the RNFL retardation alone, and the signal-to-noise ratio is improved. The actual retinal nerve fibre layer retardation is derived mathematically.¹⁹

However, if the main reason for ARP is the increased penetration of the light into the birefringent sclera,⁶ more research will be needed to study the impact of ARP on the distribution of peripapillary RNFL as determined by the new ECC algorithm.

Additional factors that contribute to the penetration of the light to the sclera are the optical properties, including reflection, pigmentation and thickness of the retinal pigment epithelium and the choroidea. The influence of these layers on the appearance of ARP has to be investigated in further studies.

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