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GDx-VCC performance in discriminating normal from glaucomatous eyes with early visual field loss

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Abstract *Background:* To evaluate the ability of scanning laser polarimetry with variable corneal compensation (GDx-VCC) in separating healthy from glaucomatous patients with early visual field (VF) loss. *Methods:* Sixty-two healthy and 48 glaucomatous age-matched patients with early glaucoma [mean deviation (MD): −1.74dB ±1.69] underwent complete ophthalmological evaluation, automated achromatic perimetry (AAP) and retinal nerve fiber layer (RNFL) measurement with GDx-VCC. One randomly selected eye from each subject was considered. Glaucomatous VF defects had either Glaucoma Hemifield Test (GHT) outside normal limits or pattern standard deviation (PSD) outside 95% confidence limits. Mean (±SD) MD, PSD and GDx-VCC parameters in the two groups were compared by *t*-test. For each GDx-VCC parameter, area under receiver operating characteristics (AUROC) curve and sensitivity at predetermined specificity ≥80% and ≥95% were calculated. Moreover, the parameter with largest AUROC was evaluated by likelihood ratios (LRs). *Results:* Mean values for MD, PSD and ten of 14 GDx-VCC parameters were significantly different between the two groups ($P<0.001$). The three parameters with largest AUROCs were the nerve fiber indicator (NFI) (0.870), superior average (0.817) and normalized superior area (0.816) ($P=0.08$ for differences between AUROCs). NFI displayed sensitivity values of 80.2% and 60.4% for specificity ≥80% and ≥95%, respectively. At NFI cutoff value of 30, positive LR was 34.9 (95% CI: 4.9–247.6) and negative LR was 0.45 (95% CI: 0.32–0.61). Interval LRs showed large effect on post-test probability for NFI values ≤18 or ≥31. *Conclusions:* In our sample of eyes with early VF loss, GDx-VCC showed moderate-to-good discriminating ability. Among the best performing parameters, NFI had the largest AUROC, but several glaucomatous eyes (21, 43.8%) had NFI <30. This suggests that algorithm for NFI calculation requires some refinement when eyes with early VF loss are evaluated.

Keywords Automated perimetry · Glaucoma · Scanning laser polarimetry

Introduction

There is increasing evidence that in most cases a structural retinal nerve fiber layer (RNFL) defect precedes the functional loss due to glaucomatous optic neuropathy [11, 16, 17, 24]. By the time a visual field (VF) defect is present on automated achromatic perimetry (AAP), as many as 40% of the retinal ganglion cell pool may be already lost [17]. In order to detect RNFL thinning at an earlier stage, in-vivo, objective, quantitative and reliable

measurements may be obtained on scanning laser polarimetry (SLP). Polarized laser light passing through tissues with physical properties of form birefringence undergoes a retardation, linearly related to thickness in a primate model [26]. The most recent generation of polarimeters (GDx-VCC) provides a customized compensation of anterior segment birefringence whose incomplete removal produced sometimes inaccurate RNFL measurements when scans were caught by instrument with fixed corneal compensator (FCC) [1, 6, 12, 27, 28]. Previous studies repeatedly confirmed that GDx-VCC have significantly improved both the structure-function relationship [18], the ability to discriminate normal from glaucomatous eyes [3, 4, 7, 14, 15, 19, 20, 22, 25], and identified RNFL thinning in perimetrically unaffected eyes of patients with unilateral glaucoma [21]. A reliable instrument, with high diagnostic accuracy would facilitate the detection of eyes with early glaucoma and an earlier diagnosis would lead to earlier treatment and increase the chance to slow or halt the disease progression at a stage where VF loss is minimal.

The aim of this study was to evaluate the diagnostic ability of GDx-VCC parameters to discriminate adequately healthy from glaucomatous eyes with early visual VF.

Materials and methods

We selected patients among those referred to the Glaucoma Unit at Trieste University Eye Clinic between January and October 2004 for periodical scheduled visit.

Criteria for inclusion in the study population were as follows:

- peripapillary RNFL thickness evaluation by means of GDx-VCC;
- good quality polarimetric images (quality score ≥8 as provided by device software)
- good quality AAP performed at ±1 month from SLP showing early glaucomatous VF loss (further details on AAP interpretation are presented later);
- refractive error within the ±4 spherical dioptres range, with less than ±2 cylinder dioptres.

Exclusion criteria were as follows:

- best corrected visual acuity ≤20/40;
- corneal or lens opacity significantly interfering with clinical, AAP or SLP examination;
- significant peripapillary atrophy falling under ellipse measurement, tilted disc, uveitis, significant vitreous floaters, diffuse or localized retinal or macular disease;
- inability to perform reliable AAP (fixation losses, false-positive or negative rates greater than 20%) or SLP (poor fixation, inattentive patients).

Each patient underwent a complete clinical examination. One single eye from each enrolled subject was selected randomly for inclusion, if both met the eligibility criteria. Best corrected visual acuity (BCVA) was measured on a standard ETDRS chart. On slit lamp, anterior segment was evaluated, and gonioscopy and Goldmann applanation tonometry performed. Optic disc was studied by stereo biomicroscopy with the aid of a +90D lens, after pupil dilation. AAP was performed with the Humphrey Field Analyzer (Humphrey Systems, Dublin, Calif., USA), 24-2 program, SITA standard strategy. Healthy subjects were recruited among staff members, friends or spouses of patients, or normal volunteers. They had all normal AAP [pattern standard deviation (PSD) within 95% confidence limits and Glaucoma Hemifield Test (GHT) within normal limits], as well as intraocular pressure <21 mmHg, healthy-looking optic disc with intact neuroretinal rim, no history of ocular disease or family history of glaucoma.

Glaucomatous optic neuropathy was defined as cupping, rim notching or diffuse thinning. On AAP, defects were classified as glaucomatous when either GHT was outside normal limits or a PSD probability of less than 5% was found. For the purpose of statistical analysis, mean deviation (MD) and PSD were considered. All glaucomatous patients had at least two previous AAP with reproducible VF defects. According to the Hodapp-Parrish-Anderson grading scale of VF defect severity, an early loss was identified by a MD <−6 dB, fewer than 25% (or 18) points depressed below 5% level and fewer than 10 points below the 1% level on pattern deviation plot, no point with sensitivity less than 15 dB in the central 5° [9].

SLP was performed with the commercially available device (GDx-VCC, software 5.3.4; Carl Zeiss Meditec, Calif., USA) using an eight-pixel-wide (approximately 0.4 mm in an emmetropic eye) circular calculation area with inner diameter of 54 pixels (approximately 2.5 mm in an emmetropic eye) centered on the optic disc. The first reading was obtained to measure and compensate anterior segment birefringence. The correct positioning of macular circle was checked after its acquisition. Then, the second reading provided values of RNFL parameters under the calculation area. Before accepting any reading, the circle correct placement on inner margin of peripapillary scleral ring was checked on the reflectance image. On both readings, maximum effort was paid to obtain high-quality scans and all eyes had to pass the four-scan quality checks

Table 1 Mean values (±SD) of age, MD, PSD in normal and glaucomatous eyes

	Normal (n=62)	Glaucomatous (n=48)	P value
Mean age (±SD), yrs	64.7±6.5	66.8±8.8	0.153
MD (±SD), dB	0.16±1.03	−1.74±1.69	<0.001
PSD (±SD)	1.42±0.60	3.56±1.5	<0.001

Table 2 Retinal nerve fiber layer measurements (mean±SD) in healthy and glaucomatous eyes on GDx-VCC

	Healthy eyes (62)	Glaucomatous eyes (48)	*P* value
NFI	19.7±5.9	39.4±17.9	<0.001*
TSNIT average (μ)	53.7±4.1	47.6±6.4	<0.001*
Superior average (μ)	64.7±5.1	55.2±8.7	<0.001*
Inferior average (μ)	60.9±6.8	53.7±9.1	<0.001*
TSNIT SD (μ)	21.7±4.3	17.2±4.8	<0.001*
Superior ratio	3.0±1.0	2.3±0.9	<0.001*
Inferior ratio	3.1±1.0	2.5±1.0	0.004
Superior/nasal	2.3±0.5	2.1±0.6	0.025
Maximum modulation	2.2±0.9	1.8±0.9	0.018
Superior maximum (μ)	74.6±8.2	64.5±12.6	<0.001*
Inferior maximum (μ)	77.4±8.7	70.9±12.3	<0.001*
Ellipse modulation	3.7±1.6	2.9±1.3	0.004
NSA	0.130±0.015	0.100±0.028	<0.001*
NIA	0.137±0.022	0.111±0.026	<0.001*

*Statistically significant at *t*-test after Bonferroni correction for multiple comparisons α is approximately 0.0036

performed by software (alignment, fixation, refraction and illumination). The operator assisted patients in keeping their heads as vertical as possible during scanning sessions in order to avoid artifacts from head tilt. The correct positioning of ellipse on inner margin of peripapillary scleral ring was rechecked on all eyes by a trained technician. Scans with evidence of atypical pattern on the printout retardation map were excluded from the study, as previously done in recent studies [15, 19].

Parameters considered were ellipse average and standard deviation (TSNIT average and SD), superior average (SA), inferior average (IA), nerve fiber indicator (NFI), superior ratio (SR), inferior ratio (IR), superior/nasal ratio (S/N), maximum modulation (MM), superior maximum (SM), inferior maximum (IM), ellipse modulation (EM), normalized superior area (NSA) and normalized inferior area (NIA). Symmetry was not considered, since in previous studies its significance resulted to be minimal [7, 14, 15, 27]. NFI is a software-generated parameter, calculated using a support vector machine algorithm based on several RNFL measures that assigns a value from 0 to 100 to each examined eye. The higher the NFI, the greater the likelihood that the eye is glaucomatous.

Mean values (±SD) of each parameter were compared by *t*-test in order to check differences between healthy and glaucomatous eyes. Bonferroni correction was applied based on the number of comparison (14 comparisons: approximately α=0.0036). For each parameter, area under the receiver operating characteristic (AUROC) curves were generated and sensitivities at fixed specificity (≥80% and ≥95%) calculated. ROC curves show the trade-off between sensitivity and 1-specificity. An AUROC curve of 1 represents perfect discrimination, whereas a 0.5 value represents chance discrimination. Differences in AUROCs were evaluated by the Hanley-McNeil method [8] and statistical significance was reached for *P* values <0.05. For NFI,

Table 3 Values of the GDx-VCC parameters with areas under the receiver operating characteristic (AUROC) curves and sensitivity at a fixed high (≥95%) and moderate (≥80%) specificity

	AUROC (SE)	Sensitivity for specificity	
		≥80%	≥95%
NFI	0.870 (0.034)	80.2	60.4
Superior average	0.817 (0.041)	68.8	58.3
NSA	0.816 (0.043)	70.8	50.0
TSNIT average	0.789 (0.044)*	66.7	56.3
TSNIT SD	0.769 (0.048)*	68.8	35.4
NIA	0.768 (0.045)*	50.0	33.3
Superior maximum	0.742 (0.050)*†	60.4	45.8
Inferior average	0.729 (0.049)*†	58.3	37.5
Superior ratio	0.711 (0.051)*†	50.0	29.2
Inferior ratio	0.678 (0.052)*†	47.9	18.8
Inferior maximum	0.669 (0.054)*†	43.8	27.1
Ellipse modulation	0.652 (0.053)*†	39.6	16.7
Maximum modulation	0.644 (0.054)*†	35.4	14.6
Superior/nasal	0.631 (0.055)*†	41.7	25.0

**P*<0.05 with respect to NFI AUROC
†*P*<0.05 with respect to NSA AUROC

Table 4 Positive and negative likelihood ratios (with 95% confidence intervals) for NFI at three different cutoff values. Interval likelihood ratios (95% confidence intervals) for NFI at different ranges of values

	NFI cut-off value		
	20	25	30
+LR (95% CI)	1.53 (1.24–1.89)	4.52 (2.5–8.2)	34.9 (4.9–247.6)
−LR (95% CI)	0.16 (0.05–0.51)	0.32 (0.21–0.52)	0.45 (0.32–0.61)
NFI range	Interval LR (95% CI)	Subjects in each category (%)	
≤18	0.07 (0.01–0.35)	21 (19.0)	
19–21	0.65 (0.30–0.98)	19 (17.3)	
22–24	0.36 (0.12–0.77)	23 (20.9)	
25–30	1.43 (0.85–31.23)	19 (17.3)	
≥31	35.2 (8.14–304.2)	28 (25.5)	

positive and negative likelihood ratios (LRs) were also calculated using the manufacturer's suggested cutoff of 30 (which is supposed to separate "within normal limits" from "borderline" eyes). LR is the probability of a given test result in those with disease divided by the probability of the same test result in those without the disease [5]. The classification of the effect of LRs of different magnitudes on the post-test probability of disease proposed by Jaeschke was used, so that a large effect on post-test probability was associated with LRs higher than 10 or lower than 0.1 [10]. Moreover, interval LRs were also calculated to weigh the effect of different NFI range values on post-test probability. In all cases LR values were provided with their 95% CI according to the method proposed by Simel [23]. Statistical analysis was performed using SPSS version 12.0 (SPSS, Chicago, Ill., USA). Each patient was fully aware about the aim of the study and signed an informed consent to participation. All methods were approved by internal Ethic Committee and adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Results

One-hundred and twenty-four eyes were considered originally, but six (4.8%) presented atypical patterns on GDx-VCC retardation map, two (1.6%) did not pass the four-scan quality check (quality score 5 or less for image illumination, due to narrow pupils), three (2.4%) saw their RNFL readings flagged as "incompatible with normative database", without any apparent reason for such a classification. Three more eyes (2.4%) did not provide enough steady fixation during the test and then were excluded.

The remaining 110 eyes (88.7%) fulfilled inclusion and exclusion criteria and then were enrolled. Among them, 62 were classified as healthy and 48 as glaucomatous, on the basis of AAP. Mean values (±SD) for MD and PSD resulted significantly different between the two groups (P<0.001, Table 1). In Table 2, mean values (±SD) for each parameter are shown separately for healthy and glaucomatous eyes. Ten out of the 14 GDx-VCC parameters were significantly different between the two groups (P<0.001 for all of them). After Bonferroni correction IR, S/N, MM and EM could not separate the two populations.

In Table 3 AUROCs (SE) for all parameters are presented, as well as sensitivity values at fixed specificity value ≥80% and ≥95%. The areas value ranged from 0.87 for NFI to 0.63 for S/N. The best performances belonged to NFI, SA and NSA, whose AUROCs did not differ significantly (P=0.08). At moderate (≥80%) and high specificity (≥95%), sensitivity ranged from 80.2% to 35.4% and from 60.4% to 14.6%, respectively. In both cases NFI had the peak values and MM the lowest ones. In Table 4, positive and negative LRs for the NFI at cutoff value of 20, 25 and 30 are shown. At a cutoff value of 20, negative LR is 0.16 (95% CI: 0.05–0.51), whereas at a cutoff value of 30 positive LR is 34.9 (95% CI: 4.9–247.6). Also in Table 4, interval LRs for different range values of the same parameter are provided. A large effect on post-test probability appears for values ≤18 or >31.

Discussion

Clinical evaluation of optic disc and AAP remain cornerstones for the diagnosis of glaucoma. Any instrumentation aiming to be added to those commonly used for detecting a disease must demonstrate its accuracy, reproducibility and high levels of both sensitivity and specificity. For glaucoma diagnosis, clinicians may be assisted by instruments that evaluate optic disc topography and peripapillary RNFL thickness. In order to state effectiveness and reliability of an instrument, a substantial agreement with AAP results should be demonstrated not only for eyes with moderate-to-severe VF loss, but also for those with early, reproducible perimetric defect. Previous studies evaluated eyes with early glaucoma by means of GDx-FCC. Bowd et al. [2] found AUROC curves ranging from 0.79 to 0.53 when diagnosis was based on AAP. Medeiros and Susanna [13] had AUROC curves ranging from 0.93 for a sectorial linear discriminant function (LDF) to 0.63 for S/N. However, if criteria for definition of early VF are strictly followed [9], mean MD values reported in those

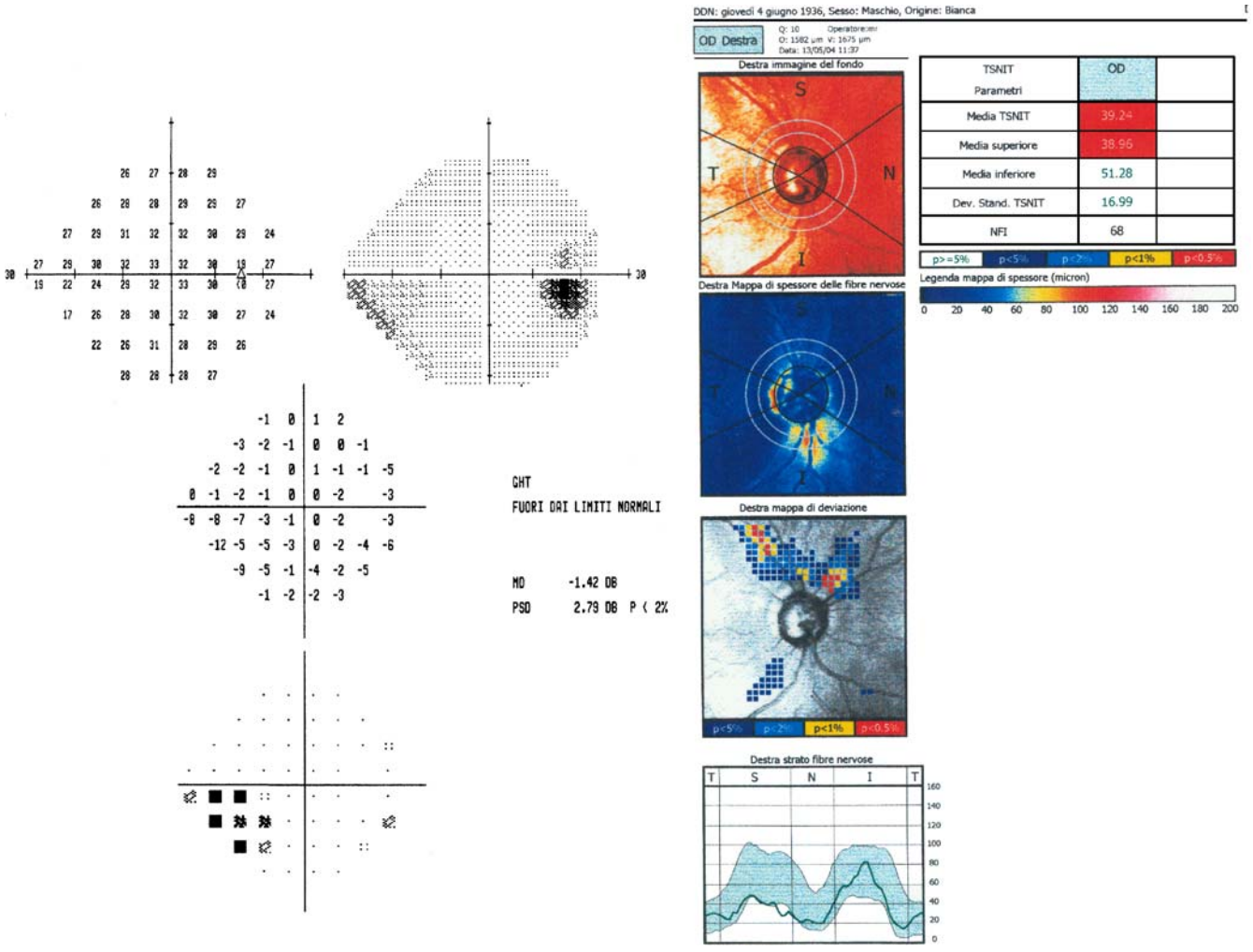

Fig. 1 AAP printout (*left*) of right eye with early VF loss in the inferior hemifield and corresponding GDx-VCC printout (*right*) with a corresponding superior bundle thinning (pixels with probability <1% and <0.5% are present). There is an initial thinning also for inferior bundle. NFI is 68

studies (−4.0±4.2 [2] and −5.32±3.81 [13] dB, respectively) indicate that authors did not include early VF defects only. On the contrary, our study included eyes with early VF loss only, for which the mean MD was −1.74 dB±1.69.

Anterior segment birefringence customized compensation improved significantly SLP diagnostic ability and structure-function relationship [3, 4, 14, 15, 18–20, 22, 25]. However, these conclusions were drawn from eyes covering the whole clinical spectrum of glaucoma severity. Recent reports described GDx-VCC performance in glaucoma populations with 25.3% and 70% of eyes with early VF loss [15, 19], respectively, but to the best of our knowledge no study describing early glaucomatous eyes only is available. The existence of a high diagnostic ability also for these patients could really support an expanded use of commercially available version of GDx-VCC for glaucoma suspects, for preperimetric glaucoma or, even, for screening procedures.

In our study, which considered age-matched healthy and glaucomatous patients with early VF loss, all parameters provided by GDx-VCC but IR, S/N, MM and EM, resulted significantly different between the two groups ($P<0.001$, *t*-test) (Table 2). Four of the new software-generated parameters (NFI, TSNIT average and SD, NSA) stand at the top five positions in the AUROC values list (Table 3). NFI had the largest AUROC (0.870), followed by the SA (0.817) and NSA (0.816) but differences in their AUROCs was not statistically significant. All other parameters' AUROCs showed values below 0.8, indicating a moderate discriminating ability. This is mostly due to the very early stage of the disease of eyes included in the study. In a previous report, after that a 30% of eyes with moderate-to-severe VF loss was added to a 70% of eyes with early a

high diagnostic ability for nine parameters was achieved and their AUROCs were ≥0.8 [15].

Considering NFI values in our glaucoma patients, there is major data spreading, since 21 eyes (43.8%) had values <30, 19 (39.6%) ≥40 and nine (18.8%) ≥60. This testifies that early VF loss may correspond to RNFL thinning of variable severity (Fig. 1). These findings have an impact on analysis conducted by LRs for the best parameter. At the manufacturer suggested cutoff value of 30, positive LR for NFI indicates a large effect on post-test probability (Table 4). On the contrary, negative LR shows a similar effect only after taking the cut-off value down to less than 20. Assessment of interval LRs indicates a large effect on post-test probability for NFI values ≤18 or >31 and values close to 1 for a range comprised between 25 and 30, indicating that these values may occur with similar probability both in healthy and in affected eyes. Then, even for the best performing parameters, there is an excessive overlapping of values, as further testified by a sensitivity never greater than 60.4% for high specificity values. Corresponding values for other parameters are even lower (Table 3).

The present study may have some limitations. The main one is the relatively small sample of glaucomatous eyes, which probably makes the results and the conclusions of a preliminary nature. A much larger sample of eyes with early VF loss could be collected in the future from different laboratories, after standardizing the selection of eyes and experimental procedures.

In conclusion, our results suggest that diagnostic ability of GDx-VCC in eyes with early VF loss is moderate-to-good. Some refinements are probably needed to improve instrument performance in this particular category of eyes. In order to achieve a better performance, three main possibilities should be considered:

1. modification of the software in order to provide the possibility of analyzing superior and inferior quadrants not only on 120°-wide sectors, but also on smaller zones, as previously done (four sectors, approximately 39.4°-wide, on GDx-VCC [20]; 16 sectors, 22.5°-wide, on GDx-FCC [13]) in order to reduce chances to miss early RNFL localised thinning;
2. define a standardized procedure to interpret the whole GDx-VCC printout, going beyond the numerical values of single parameters;
3. creation of a linear discriminant function (LDF) containing the most meaningful parameters.

Through these refinements and after further research, clinicians would probably benefit entirely from the potential of GDX-VCC, especially when achievement or confirmation of early glaucoma diagnosis is needed.

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