EXTENDED REPORT

Detection of glaucoma using operator-dependent versus operator-independent classification in the Heidelberg retinal tomograph-III

N Harizman, J R Zelefsky, E Ilitchev, C Tello, R Ritch, J M Liebmann

Br J Ophthalmol 2006;**90**:1390–1392. doi: 10.1136/bjo.2006.098111

See end of article for authors' affiliations

Correspondence to: J M Liebmann, Department of Ophthalmology, New York University School of Medicine, 310 East 14th Street, Suite 304, New York, NY 10003, USA; jml18@earthlink.net

Accepted 4 July 2006
Published Online First 26 July 2006

Objective: To compare the abilities of a new Glaucoma Probability Scoring (GPS) system and Moorfields regression analysis (MRA) to differentiate between glaucomatous and normal eyes using Heidelberg retinal tomograph (HRT)-III software and race-specific databases.

Methods: In this prospective study, one eye (refractive error $\leqslant$5 D) each of consecutive normal patients and those with glaucoma was enrolled. All patients underwent a full eye examination, standard achromatic perimetry (Swedish Interactive Threshold Algorithm-standard automated perimetry (SITA-SAP), program 24-2) and confocal scanning laser ophthalmoscopy (HRT-II) within 1 month. Normal patients had two normal visual fields in both eyes (pattern standard deviation (PSD) $>$5% and Glaucoma Hemifield Test within 97% normal limits) and a normal clinical examination. Glaucoma was defined on the basis of SITA-SAP visual field loss (PSD$<$5% or Glaucoma Hemifield Test outside normal limits) on two consecutive visual fields. HRT-II examinations were exported to the HRT-III software (V.3.0), which uses an enlarged race-specific database, consisting of 733 eyes of white people and 215 eyes of black people. Race-adjusted MRA for the most abnormal sector (operator-dependent contour line placement) was compared with the global race-adjusted GPS (operator independent). MRA sectors outside the 99.9% confidence interval limits (outside normal limits) and GPS $\geqslant$0.64 were considered abnormal.

Results: 136 normal patients (72 black and 64 white patients) and 84 patients with glaucoma (52 black and 32 white patients) were enrolled (mean age 50.4 (SD 14.4) years). The average visual field mean deviation was −0.4 (SD 1.1) db for the normal group and −7.3 (SD 6.7) db for the glaucoma group ($p<0.001$). Mean GPS values were 0.21 (SD 0.23) and 0.73 (SD 0.27) for normal and glaucomatous eyes, respectively ($p<0.001$). Sensitivity and specificity values were 77.1% and 90.3% for GPS, and 71.4% and 91.9% for MRA, respectively.

Conclusions: In this cohort, GPS software sensitivity and specificity values are similar to those of MRA, which requires placement of an operator-dependent contour line. The development of software to detect glaucoma without a contour line is critical to improving the potential use of HRT as a tool for glaucoma detection and screening.

Primary open-angle glaucoma is a leading cause of blindness worldwide.[1] Glaucomatous changes to the optic nerve head and retinal nerve fibre layer (RNFL) loss often precede achromatic visual field defects, which may become manifest only after a large percentage of retinal ganglion cells have been damaged.[2 3] As such, early disease detection may be important in disease management strategies. Confocal scanning laser ophthalmoscopy has become an important tool for detecting structural damage of the optic nerve head and RNFL, and may assist in early glaucoma detection.[4 5] There seem to be important racial differences between people of African and European ancestry regarding optic disc configuration[6–11] and neuroretinal rim area.[12 13] Given these variations, questions exist as to whether the current Heidelberg Retinal Tomograph (HRT)-II database of people of European ancestry can be applied to other racial groups.[10]

Heidelberg retinal tomography (Heidelberg Engineering, GmBH, Dossenheim, Germany) uses confocal scanning laser technology to calculate topographic measurements of the optic nerve and parapapillary RNFL. One method of the HRT-II software analysis, Moorfields regression analysis (MRA), uses an algorithm to compare measured optic nerve parameters with those from a normative database.[9] Although there is good reproducibility of HRT measurements,[14–16] a major limitation of this device is the need for an operator to draw a contour line at the border of the optic disc. This can result in variability in measurements between different observers.[17] The HRT-II uses a normative database consisting of 349 normal eyes of white people, whereas HRT-III uses an enlarged race-specific database, consisting of eyes of 733 white and 215 black people (Heidelberg Engineering, personal communication, Heidelberg Engineering, 2006).

HRT-III software V.3.0 includes the calculation of the Glaucoma Probability Score (GPS), a new, automated algorithm that evaluates both optic disc and parapapillary RNFL topography to estimate the probability of having glaucoma. The GPS uses two measures of parapapillary RNFL shape (horizontal and vertical RNFL curvature) and three measures of optic nerve head shape (cup size, cup depth and rim steepness) for input into a vector machine-learning classifier that estimates the probability of having damage consistent with glaucoma. No contour line or reference plane is used in the GPS calculation, and therefore the analysis is operator independent. This is based on mathematical modelling of the optic nerve shape, which typically exhibits a cup

Abbreviations: GPS, Glaucoma Probability Score; HRT, Heidelberg retinal tomograph; MFC, Moorfields classification; MRA, Moorfields regression analysis; RNFL, retinal nerve fibre layer

Table 1 Patient demographics and mean values

	Normal	Glaucoma	p Value*
Total = n (W, B)	134 (62 W, 72 B)	83 (31 W, 52 B)	
Age, years†	45.5 (13.6)	58.5 (11.8)	<0.001
Visual field mean deviation, db†	−0.40 (1.05)	−7.31 (6.66)	<0.001
Range	2.00 to −2.84	1.22 to −30.51	
Visual field pattern standard deviation, db†	1.44 (0.25)	6.58 (3.85)	<0.001
Range	0.99 to 1.99	1.66 to 17.19	
Global GPS%†	21.25 (23.36)	73.19 (27.11)	<0.001

B, black patients; GPS, Glaucoma Probability Score; W, white patients.
*p Value by Student's t test.
†Values are mean (SD).

with varying width and depth, as well as curvature of the rim region.[18] The normally convex RNFL curvature, caused by the ganglion cell axons converging towards the optic nerve, flattens as axons are lost as a result of glaucoma.

In the present study, we compared the abilities of GPS and MRA to differentiate between glaucomatous and normal eyes using HRT-III software and race-specific databases.

METHODS

Institutional Review Board approval was obtained and all participants provided signed informed consent. Normal people, those suspected of having glaucoma and patients with glaucoma aged ⩾18 years were enrolled. All participants had a best-corrected visual acuity of at least 20/40 in the study eye, spherical refractive error ⩽5.0 D and cylinder correction ⩽3.0 D. Patients with anatomically narrow angles, retinal disease, considerable ocular surface disease, non-glaucomatous optic neuropathy or a history of intraocular surgery other than uncomplicated cataract surgery were excluded. If both eyes were eligible, one eye of each participant was randomly enrolled.

All participants underwent a complete ophthalmic examination, which included a review of relevant medical history, best-corrected visual acuity, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated funduscopy, stereoscopic ophthalmoscopy of the disc using a 78-D lens, and simultaneous stereoscopic photographs of the optic disc. Two baseline standard achromatic perimetry examinations (Swedish Interactive Threshold Algorithm-standard automated perimetry, program 24-2, Humphrey Field Analyzer II; Carl Zeiss Meditec, Dublin, California, USA) and confocal scanning laser ophthalmoscopy (Heidelberg Retinal Tomograph II; HRT-II Heidelberg Engineering) were carried out within 1 month of enrolment. All participants had reliable visual field test results, defined as <33% false-positive errors, false-negative errors and fixation losses.

For HRT-II imaging, a mean topographic image was automatically obtained from three scans (10° field of view), centred on the optic disc using HRT-II software V.1.4.1. Corneal curvature measurements were recorded using keratometry to correct for magnification error. Good image quality was defined as follows: acquisition sensitivity <90%, topography standard deviation (SD) <40 μm, more than three quarters of the disc within the target circle, minimal movement during the acquisition movie, no floaters over the disc, and good imaging clarity and exposure. A trained technician, relying on stereophotographs of the respective optic disc, outlined the optic disc margin on the mean topographic image.

Racial groups were defined by self-report. Glaucoma was defined by the existence of reproducible standard automated perimetry loss (pattern standard deviation <5% or Glaucoma Hemifield Test outside normal limits) on two consecutive fields. Participants were considered to be normal if both visual fields in both eyes were unremarkable (pattern standard deviation >5% and Glaucoma Hemifield Test within 97% normal limits) and the clinical examination was normal. HRT-II data results were exported to the HRT-III software (V.3.0) and the appropriate racial database was selected before analysis. Moorfields regression analysis (MRA) for the most abnormal sector Moorfields Classification (MFC) result (operator dependent) was compared with the global GPS (operator independent). Sectors outside the 99.9% confidence interval limits (outside normal limits) were determined to be abnormal. Sectors declared normal or borderline were considered to be normal. As per the manufacturer's recommendations, a GPS of ⩾0.64 was considered to be outside normal limits with an approximate sensitivity and specificity of 70% and 90%, respectively.

Data were statistically analysed using JMP (SAS Institute, Cary, North Carolina, USA). Student's t test was used to compare the distributions of continuous variables between groups. Values of $p<0.05$ were regarded as significant. Sensitivities and specificities were calculated for race-adjusted MRA-III MFC result (result of the worst sector) and for global GPS results.

Table 2 Sensitivity and specificity of Moorfields and Glaucoma Probability Score classifications

	MFC result HRT-III	Global GPS
Sensitivity	71.1% (59/83)	77.1% (64/83)
Sensitivity for early glaucoma	59.6% (28/47)	72.3% (34/47)
Specificity	91.8% (123/134)	90.3% (121/134)

GPS, Glaucoma Probability Score; MFC, Moorfields classification.
MFC Result HRT-III: the worst sector in the race-adjusted MFC analysis.
Global race-adjusted GPS: Early glaucoma, mean deviation ⩽−5 db.

RESULTS

In all, 136 (72 black and 64 white) normal patients and 84 (52 black and 32 white) patients with glaucoma were enrolled. Three participants were excluded from the final analysis because the software failed to calculate GPS values. Mean (SD) age was 50.4 (14.4) years (45.5 (13.6) and 58.5 (11.8) years for normal patients and for those with glaucoma, respectively; $p<0.001$; table 1). The mean (SD) visual field mean deviation was −0.40 (1.05, range 2.00 to −2.84) db for normal eyes and −7.31 (6.66, range 1.22 to −30.51) db for glaucomatous eyes ($p<0.001$). The mean (SD) visual field pattern was 1.44 (0.25, range 0.99–1.99) db for normal eyes and 6.58 (3.85, range 1.66–17.19) db for glaucomatous eyes ($p<0.001$).

The GPS model could not be calculated in 3 of the 220 patients (two normal patients and one with glaucoma); these patients were excluded from the final analysis. GPS fails to calculate the model as a result of absence of an optic cup or due to very small disc size, which was seen in two of our patients in whom disc sizes were 0.872 and 0.953 mm. The

HRT-III MFC result analysis detected glaucoma in 59 of the 83 glaucomatous eyes, yielding a sensitivity of 71.1%; it confirmed normal tests in 123 of 134 normal eyes, yielding a specificity of 91.8%. Global GPS analysis detected glaucoma in 64 of the 83 glaucomatous eyes, yielding a sensitivity of 77.1%, and confirmed normal tests in 121 of 134 normal eyes, yielding a specificity of 90.3% (table 2).

Further analysis was carried out on a subgroup of 47 patients with early glaucoma, defined as mean deviation on visual field $\leqslant -5$ db. As shown in table 2, sensitivity levels decreased in early glaucoma for both MRA and GPS (59.6% and 72.3%, respectively).

DISCUSSION

Computerised optic nerve imaging is often used to augment traditional methods of optic disc examination in the management of glaucoma. The HRT ancillary study to the Ocular Hypertension Study proved the ability of confocal laser ophthalmoscopy to identify early glaucomatous injury and predict the conversion from ocular hypertension to glaucoma using the Ocular Hypertension Study criteria.[5] One limitation of HRT technology has been the need to place an operator-dependent contour line at the border of the optic disc before computerised analysis. Iester *et al*[17] reported that even in ideal circumstances, outlining the optic disc with the aid of optic disc photographs, intraobserver variability cannot be entirely eliminated.

We assessed the ability of the new HRT-III software to differentiate between normal and glaucomatous eyes. This software takes advantage of an enlarged race-specific database and a machine-learning classifier to help better identify glaucoma. GPS without the use of an operator-dependent contour line successfully differentiated glaucomatous eyes from normal ones, with sensitivity and specificity levels comparable to those in MRA.

GPS was better at detecting patients with early glaucoma (mean deviation $\leqslant -5$ db), with a sensitivity of 72.3% compared with 59.6% for MRA. As it is difficult to place the contour line accurately, particularly in a fast-paced general ophthalmology setting, sensitivity and specificity of MRA in clinical practice are likely to be less than we reported herein, and thus the benefits of an operator-independent system such as the GPS will be more evident.

A global parameter of the GPS performed as well or even better than any abnormal individual MRA sector for detecting glaucoma. Interestingly, a global parameter was sufficient for discriminating healthy and glaucomatous eyes; the diagnostic accuracy of these algorithms should be tested in future studies.

In summary, the GPS of the HRT-III represents an alternative strategy for diagnosing glaucoma, with a considerable advantage over the MRA in early stages of the disease. The GPS bypasses the ''Achilles heel'' of the HRT, which is the need for an operator-dependent contour line. Automated image analysis free of contour line placement suggests that the HRT-III may have a role in glaucoma detection and screening.

Authors' affiliations

N Harizman, E Ilitchev, C Tello, R Ritch, Departments of Ophthalmology, New York Eye and Ear Infirmary, New York, New York, USA
J R Zelefsky, Department of Ophthalmology, New York University School of Medicine, New York, USA
J M Liebmann, Manhattan Eye, Ear and Throat Hospital, Manhattan, New York, USA

Funding: This study was supported in part by the Shelley and Steven Einhorn Research Fund of the New York Glaucoma Research Institute, New York, USA.

Competing interests: None.

Presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, USA, May 2006.

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