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Diagnostic accuracy of the Moorfields Regression Analysis using the Heidelberg Retina Tomograph in glaucoma patients with visual field defects

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Purpose. *This study was designed to determine the specificity and sensitivity of the Heidelberg Retina Tomograph I (HRT) using the Moorfields Regression Analysis (MRA) in differentiating healthy from glaucomatous eyes.*
Methods. *In this cross-sectional study, 74 eyes of 37 healthy subjects and 87 eyes of 47 glaucoma patients were examined with Octopus standard automated perimetry and HRT. Only one eye per patient was used for statistical analysis. According to visual field index mean defect (MD) glaucoma patients were divided into three groups with early (MD <6 dB), moderate (6 dB < MD <12 dB), and advanced visual field loss (MD >12 dB). The sensitivity and specificity of optic nerve head examinations using the MRA of HRT were evaluated by two criteria (criteria 1, as diseased if classified by MRA as outside normal limits; criteria 2, as diseased if classified by MRA as borderline). The correlations between the topographic parameters and visual field index MD were measured by correlation coefficient and presented by scatter plot.*
Results. *The specificity and sensitivity of HRT-MRA examination were, respectively, 100% and 68.1% when borderline cases were considered normal (criteria 1) and 97.3% and 85.1% when borderline cases were considered glaucomatous (criteria 2). The sensitivity of the MRA in eyes with different stages of visual field loss was 59.1% for early, 54.5% for moderate, and 92.8% for advanced visual field loss with criteria 1; the figures were, respectively, 81.8%, 72.7%, and 100% with criteria 2. The statistically significant correlations with moderate strength of association (r=0.40–0.59) were found for rim area, rim volume, cup to disc area ratio, mean retinal nerve fiber layer (RNFL) thickness, and RNFL cross-sectional area.*
Conclusions. *The MRA showed an excellent specificity and good sensitivity using criteria 2 including as glaucomatous optic discs those classified by MRA as borderline. Although correlations of moderate strength were found between rim area, rim volume, mean RNFL thickness, RNFL cross-sectional area, and visual field index MD, great interindividual variation limits the prediction of one parameter from the other. Therefore, in clinical practice both structural and functional examinations should be performed in order to characterize glaucomatous damage. (Eur J Ophthalmol 2007; 17: 216-22)*

Key Words. *Glaucoma, Heidelberg retina tomograph, Moorfields regression analysis*

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INTRODUCTION

Glaucoma is progressive optic neuropathy with loss of retinal ganglion cells and their axons, leading to loss of vision (1). Functional losses are usually assessed with standard automated perimetry and may be preceded by structural changes of the optic disc and retinal nerve fiber layer (2). Structural losses at the optic disc may be evaluated in a subjective way (ophthalmoscopy, planimetry), which shows high interobserver variation. Confocal scanning laser ophthalmoscopy with the most frequently used Heidelberg Retina Tomograph (HRT) (Heidelberg Engineering GmbH, Dossenheim, Germany) enables more quantitative and objective analysis of optic disc changes. It was shown for various HRT parameters such as cup shape measure (3), the ratio of hemipapillary rim volumes, the total rim area, and the cup-disc area ratio to improve the precision of glaucoma diagnosis (4). The multivariate discriminant analysis included in the HRT I classified the eyes as glaucomatous or normal on the basis of three predefined HRT parameters: rim volume, height variation contour, and cup shape measure, adjusted for age (5). The latest software implemented in the HRT II, the Moorfields Regression Analysis (MRA), takes into account global and sectorial rim area adjusted for disc size and age. It was shown to better separate patients with early glaucoma from normal subjects (6).

The aim of this study was to evaluate the specificity and sensitivity of the MRA in our population of patients with glaucoma with different stages of visual field loss and to investigate the correlation between visual field index mean defect (MD) and optic nerve head topographic parameters.

METHODS

The research adhered to the tenets of the Declaration of Helsinki and was approved by the national ethics committee.

Thirty-seven healthy subjects and 47 patients with glaucoma were recruited for the study (Tab. I). All eyes had better visual acuity than 0.5, refractive error less than ±6 diopters, clear optic media, and no optic disc anomaly

TABLE I - CHARACTERISTICS OF THE STUDY POPULATION

Parameter	Normal (n=37)	Glaucoma (n=47)	p*
Age, yr (mean ± SD)	55.5±9.5	66.9±9.5	0.03
Male (%)	20 (54)	24 (51)	NS
Mean defect ± SD (dB)	–0.06±1.20	8.2±7.1	<0.001
Loss variance ± SD (dB)	1.43±1.16	23.9±22.0	<0.001

*Student t-test. SD = Standard deviation

TABLE II - VALUES OF HRT MEASUREMENTS IN 37 HEALTHY AND 47 GLAUCOMATOUS EYES

Parameter (unit)	Normal mean (SD)	Range	Glaucoma mean (SD)	Range	p*
Disc area (mm^2)	1.97 (0.41)	1.43–3.32	2.16 (0.46)	1.39–3.304	0.056
Cup area (mm^2)	0.32 (0.25)	0.0–0.90	1.13 (0.51)	0.20–2.48	<0.001
Rim area (mm^2)	1.65 (0.37)	1.08–2.48	1.03 (0.40)	0.30–2.50	<0.001
Cup volume (mm^3)	0.05 (0.06)	0.0–0.22	0.33 (0.29)	0.0–1.55	<0.001
Rim volume (mm^3)	0.48 (0.19)	0.15–1.10	0.23 (0.17)	0.03–1.01	<0.001
C/D area ratio	0.16 (0.11)	0.0–0.37	0.51 (0.19)	0.0–0.84	<0.001
Mean cup depth (mm)	0.16 (0.07)	0.03–0.37	0.31 (0.15)	0.02–0.66	<0.001
Max. cup depth (mm)	0.43 (0.18)	0.10–0.92	0.65 (0.24)	0.07–1.30	<0.001
Cup shape measure	–0.15 (0.06)	–0.27–0.0	–0.05 (0.09)	–0.26–0.17	<0.001
Height variation contour (mm)	0.40 (0.09)	0.22–0.57	0.35 (0.10)	0.17–0.61	<0.001
Mean RNFL thickness (mm)	0.26 (0.06)	0.16–0.38	0.17 (0.08)	–0.01–0.38	<0.001
RNFL cross-sectional area (mm^2)	1.29 (0.33)	0.70–2.00	0.88 (0.45)	0.05–2.06	<0.001

*Mann-Whitney U test. HRT = Heidelberg Retina Tomograph; SD = Standard deviation; RNFL = Retinal nerve fiber layer (e.g., tilted discs, drusen of the disc). Healthy subjects older than 40 years were recruited from the outpatients requiring presbyopic correction. Inclusion criteria were no history of eye disease, intraocular pressure <21 mmHg, normal findings in an eye examination, and a reliable visual field with normal findings (Octopus perimeter 101, Tendency Oriented Perimetry [TOP], glaucoma program G2).

Patients with glaucoma were referred from the glaucoma unit of the Eye Hospital Ljubljana. Inclusion criteria were intraocular pressure at diagnosis >21 mmHg, open angles on gonioscopy, and a reproducible visual field defect in the absence of any other abnormalities to explain the defect.

Visual field testing was performed with Octopus 101 perimeter, glaucoma program G2, TOP strategy. Visual fields had to be reproducible and reliable with false positive and false negative response rates less than 15%. In glaucomatous eyes with advanced visual field loss, a negative response rate up to 33% was accepted. A glaucomatous visual field defect was defined as three abnormal points on two consecutive tests, with p<5% probability of being normal, one of which should have p<1%, all being not contiguous with the blind spot, localized in the superior or inferior arcuate area, paracentral area, or as a nasal step.

The visual fields were graded on the basis of mean defect (MD) as mild (MD<6 dB), moderate (6 dB<MD<12 dB), and advanced or severe visual field loss (MD>12 dB).

After optic disc photography with nonmydriatic fundus camera (Topcon TRC–NW6S) and keratometry, optic disc imaging was performed with HRT I in all subjects after dilation of pupils. Before each measurement the subject's refractive error and corneal curvature were entered into the software (version 3.0). Three high quality images at a scan angle of 10 degrees were recorded for each subject to obtain mean topography image. Optic nerve head image was recreated from a series of optical sections cut at 32 consecutive focal planes, and the information displayed in the topographic and reflectivity image. The optic disc margin was outlined manually at the inner edge of Elschnig ring while looking at the optic disc photograph. The standard reference plane was used for calculations of 12 optic disc parameters.

The HRT classification of optic disc was determined according to MRA, which is based on the relationship between global and sectorial optic disc area and rim area, adjusted for age. By comparing the actual measurements for the global and six optic disc segments to the database obtained from 112 normal eyes and 77 eyes with early glaucoma the MRA classifies optic disc into three grades:

TABLE III - SPECIFICITY AND SENSITIVITY OF THE MOORFIELD REGRESSION ANALYSIS (MRA)

MRA	Normal eyes (n=37) Positive	Normal eyes (n=37) Negative	Glaucoma eyes (n=47) Positive	Glaucoma eyes (n=47) Negative
Criteria 1	0	37	32	15
Criteria 2	1	36	40	7
MRA	**Specificity**		**Sensitivity**	
Criteria 1	100.0%		68.1%	
Criteria 2	97.3%		85.1%	

Criteria 1 = Positive if classified as outside normal limits; Criteria 2 = Positive if classified as borderline

TABLE IV - SENSITIVITY OF THE MOORFIELDS REGRESSION ANALYSIS (MRA) AT DIFFERENT STAGES OF VISUAL FIELD LOSS IN 47 PATIENTS WITH GLAUCOMA

Visual field loss	MRA classification Criteria 1		MRA classification Criteria 2		Sensitivity Criteria 1	Sensitivity Criteria 2
Early (n=22)	13 pos.	9 neg.	18 pos.	4 neg.	59.1%	81.8%
Moderate (n=11)	6 pos.	5 neg.	8 pos.	3 neg.	54.5%	72.7%
Advanced (n=14)	13 pos.	1 neg.	14 pos.	0 neg.	92.8%	100%

Criteria 1 = Positive if classified as outside normal limits; Criteria 2 = Positive if classified as borderline; Early = MD < 6 dB; Moderate = 6 dB < MD < 12 dB; Advanced visual field loss = MD > 12 dB; Pos. = Positive outcome; Neg. = Negative outcome

TABLE V - CORRELATION BETWEEN HRT PARAMETERS AND VISUAL FIELD INDEX MEAN DEFECT (MD) IN THE GLAUCOMA GROUP

HRT parameters	MD	
	Correlation coefficient (r)	p value
Disc area	–0.07	0.63
Cup area	0.28	0.06
Rim area	–0.45	0.002
Cup volume	0.08	0.59
Rim volume	–0.43	0.003
C/D area ratio	0.40	0.005
Mean cup depth	–0.13	0.37
Max. cup depth	–0.19	0.20
Cup shape measure	0.15	0.31
Height variation contour	–0.08	0.57
Mean RNFL thickness	–0.48	0.001
RNFL cross-sectional area	–0.48	0.001

HRT = Heidelberg Retina Tomograph; r = Spearman correlation coefficient; p = Statistically significant at $p<0.05$; C/D = Cup to disc; RNFL = Retinal nerve fibre layer

normal if all the measurements fall within 95% confidence intervals (CI); borderline if at least one falls between the lower 95% and 99.9% CI; and outside normal limits if at least one measurement is less than the lower 99.9% CI. To evaluate the diagnostic accuracy of the MRA we used two criteria: criteria 1, the optic disc was defined as glaucomatous if at least one measurement was labeled outside normal limits; criteria 2, the optic disc was considered glaucomatous if at least one measurement was labeled borderline.

Only one eye (left eye) per subject was included; in six glaucoma patients the left eye was unaffected and the only diseased eye was used in analysis. Sensitivity and specificity were expressed following the two criteria. The positive and negative predictive value of the MRA was calculated. The positive predictive value represents the proportion of test-positive subjects who truly have the disease. Conversely, the negative predictive value represents the proportion of test-negative subjects who truly do not have the disease. For topographic parameters measured by HRT mean, standard deviation, and range were calculated. The differences between the control and glaucoma group were determined by Mann-Whitney *U* test. The correlation between optic disc topographic parameters and visual field index mean defect was assessed with nonparametric Spearman rank correlation coefficient and linear regression analysis. The software SPSS for Windows, version 12.0 (SPSS, Chicago, IL, USA) was used to perform statistical analysis.

RESULTS

In Table II values of HRT measurements in healthy and glaucomatous eyes are presented. There were significant differences between the two groups in all optic disc parameters except in the disc area (p=0.056). The specificity and sensitivity of MRA using both criteria is presented in Table III. Sensitivity of MRA at different stages of visual loss (Tab. IV) improved when borderline outcomes were treated as positive (criteria 2) especially in eyes with early visual field loss.

With an estimated prevalence of glaucoma of 2.5% among the Caucasian population (7) and sensitivity of 85.1% the predictive value of an abnormal (borderline) examination would be 43.5%. Because the prevalence of glaucoma is low and the specificity 97.3% the negative predictive value is 99.5%.

The correlation between visual field index mean defect and topographic parameters was found to be significant for several optic disc parameters (Tab. V). Although the statistics revealed moderate asso-ciations (r = 0.4 to 0.6) of the rim area, rim volume, cup to disc area ratio, mean retinal nerve fiber layer thickness, and retinal nerve fiber layer cross-sectional area with visual field mean defect (MD), the scatter plots show great interindividual variation of the topographic parameters at the same visual field defect (Figs. 1–3).

DISCUSSION

We investigated the diagnostic accuracy of the MRA to separate normal from glaucomatous eyes with different stages of visual field loss. The specificity and sensitivity of MRA were 100% and 68.1%, respectively, with the criteria 1 (borderline outcomes considered normal) and 97.3% and 85.1% with the criteria 2 (borderline outcomes considered glaucomatous).

In other studies the reported specificities for the MRA algorithm with criteria 1 ranged from 94% to 96% and sensitivities from 58% to 84% (6, 8-10). When treating borderline cases as test positives the MRA specificity and sensitivity were 81% and 78%, respectively (9).

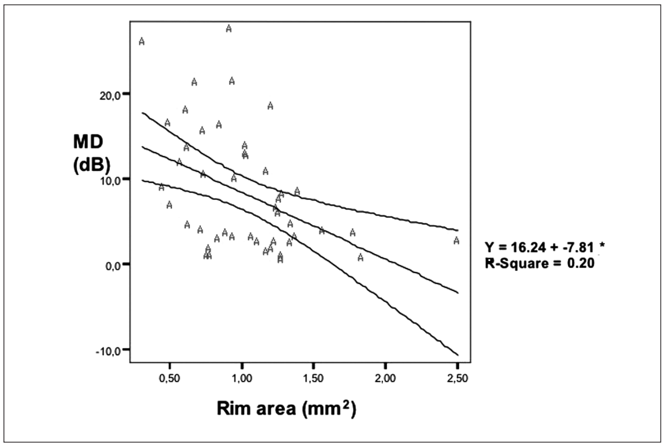

Fig. 1 - *Scatter plot of the relation between mean defect (MD) by Octopus perimetry and rim area (linear regression with 95% confidence interval).*

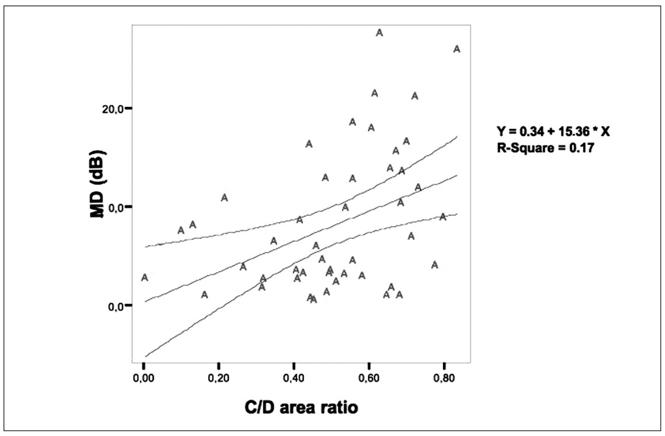

Fig. 2 - *Scatter plot of the relation between mean defect (MD) by Octopus perimetry and cup to disc area ratio (linear regression with 95% confidence interval).*

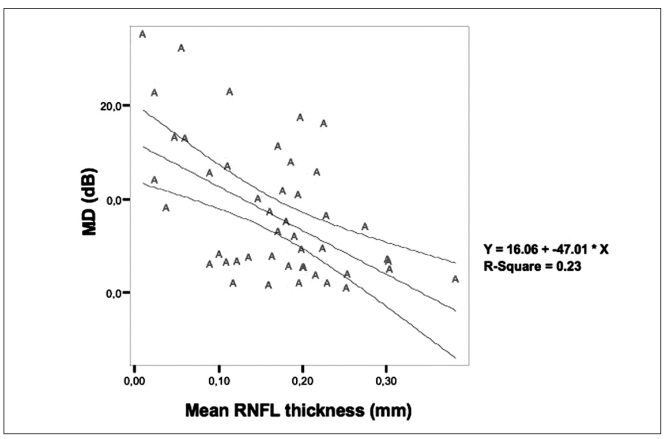

Fig. 3 - *Scatter plot of the relation between mean defect (MD) by Octopus perimetry and mean retinal nerve fibre (RNFL) thickness (linear regression with 95% confidence interval).*

Different discriminating ability of the MRA could be due to difference in the study population, its age, and severity of the disease. Some studies found that age was not associated with any disc characteristics (11, 12) whereas another study (13) showed that cup and disc area as well as cup to disc area ratio increased with age whereas the RNFL thickness decreased. With greater disc size in elderly subjects reduced specificity of the MRA is expected (10, 14, 15).

Because our normal data appear similar to the data on which the MRA is based, high diagnostic accuracy is expected. Despite the high sensitivity with criteria 2 (borderline cases considered glaucomatous), there was a considerable difference in the visual field loss, which was greater in our glaucoma patients (mean MD 8.2 dB versus 3.6 dB) than in the study by Wollstein et al (6) and therefore better sensitivity would be anticipated. The reason for this may be different population of patients with glaucoma with larger optic disc size than in the control group. Larger disc area in the glaucoma group is accompanied by larger values of optic disc size dependent parameters with increased variability and hence wider confidence intervals. Good discriminating ability of the HRT (the recom-mendation of the producer) is for the optic disc size between 1.2 and 2.8 mm^2. However, three patients in the glaucoma group had a disc size greater than 2.8 mm^2 (2.9 mm^2 to 3.3 mm^2), but the MRA classified all the eyes correctly as outside normal limits. Larger optic discs were associated with increased sensitivity of the MRA (15) and of various HRT parameters (5, 14, 16). Although in discriminating normal from glaucomatous eyes the MRA takes into account the optic disc size when evaluating the rim area, it was shown that large discs (area > 2.10 mm^2) were still classiffied with a higher sensitivity but lower specificity than small discs (area < 1.73 mm^2) (9).

The sensitivity of MRA was highest with advanced glaucoma defined as mean defect greater than 12 dB. This was also demonstrated by Medeiros et al (16) that the severity of visual field loss had a significant influence on the sensitivity of several imaging instruments (HRT II, GDx VCC, and OCT). More severe disease was associated with increased sensitivity. The sensitivity in our study was surprisingly better in the eyes with early (59% with criteria 1 and 81.8% if borderline outcome was considered positive - criteria 2) than moderate glaucoma (54.5 % criteria 1 and 72.7% criteria 2). The reason may be the smaller number of eyes with moderate glaucoma (n=11) than with early glaucoma (n=22). Also the eyes with early glaucoma had significantly larger optic discs (mean disc area 2.25 mm^2, range 1.44 mm^2 to 3.30 mm^2) than eyes with moderate glaucoma (mean disc area 1.92 mm^2, range 1.39 mm^2 to 2.38 mm^2; p=0.04) which as mentioned previously (16) may have increased the sensitivity. Other authors (8) reported fairly constant sensitivity of MRA of 66% when mean deviation was within −12 dB, and increased to 92% when MD was larger.

Statistically significant correlations were found between visual field index MD and rim area, rim volume, cup to disc area ratio, mean RNFL thickness, and RNFL cross-sectional area, but the strength of the association was moderate (r=0.40 to 0.59). Other studies reported significant correlation of MD with rim area (17, 18), rim volume (18), mean RNFL thickness, RNFL cross-sectional area, and cup shape measure with the strongest association (r=0.62) between MD and rim area (19). Rim area was also reported to be the most important predictor for diffuse and localized visual field loss (20).

In our scatter plots, for a certain rim area value there was a large range of values for the corresponding visual field index MD. The large intersubject variability, most pronounced in the eyes with early and moderate glaucoma, weakens the relation between functional and structural data. The dependence of the MD on the topographic parameter measured by R-square was highest (R^2=0.23) for the mean RNFL thickness and RNFL cross-sectional area, which means that only 23% of the variation in MD can be explained by these topographic parameters.

Our data suggest that by treating borderline outcomes as positive (criteria 2) MRA has good diagnostic accuracy, but the usefulness of MRA-HRT for screening is limited by low positive predictive value of 43.5%. This means that for every correctly identified glaucoma patient, two subjects will have to be examined.

In conclusion, in our population when borderline cases were considered positive MRA had excellent specificity and good sensitivity and adds important information in the clinical setting. Because of great variability between eyes with early and moderate glaucoma both structural and functional examinations should be performed in order to characterize glaucomatous damage.

None of the authors has any proprietary interest.

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