·Clinical Research·

Agreement in identification of glaucomatous progression between the optic disc photography and Heidelberg Retina Tomography in young glaucomatous patients

Paraskeva Hentova-Sencanic [1,2], Ivan Sencanic [3], Goran Trajkovic [4], Marija Bozic [1,2], Nevena Bjelovic [5]

[1]Faculty of Medicine, University of Belgrade, Dr Subotica 8, Belgrade 11000, Serbia
[2]Clinic for Eye Diseases, Clinical Center of Serbia, Pasterova 2, Belgrade 11000, Serbia
[3]Clinic for Eye Diseases, University Medical Centre Zvezdara, Dimitrija Tucovica 161, Belgrade 11000, Serbia
[4]Insitute of Statistics, Faculty of Medicine, University of Belgrade, Serbia, Dr Subotica 8, Belgrade 11000, Serbia
[5]Center for Vision Oftalmika, Strahinjica bana 78, Belgrade 11000, Serbia
Correspondence to: Paraskeva Hentova-Sencanic. Clinic for Eye Diseases, Clinical Centre of Serbia, Pasterova 2, Belgrade 11000, Serbia. ivama@orion.rs
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Abstract

• AIM: To evaluate concordance between the clinical assessment of glaucomatous progression of the optic disc photography and progression identified by Heidelberg Retina Tomograph (HRT) in patients with suspected primary juvenile open angle glaucoma(JOAG).

• METHODS: Optic disc photographs and corresponding HRT ‖ series were reviewed. Optic disc changes between first and final photographs were noted as well as progression identified by HRT topographic change analysis (TCA) and rim area regression line (RARL) Agreement between progression indentified by photography and HRT methods was assessed. Progression, determined from optic disc photographs by consensus assessment was used as the reference standard.

• RESULTS: A total of 31 patients (59 eyes) with suspected JOAG were studied. Agreement for progression/no progression between TCA and photography was obtained in 4 progressing eyes and 38 stable eyes (71.19%, k=0.11). Agreement for progression/ no progression between RARL and photography was detected in 5 progressing eyes and in 34 stable eyes (66.10%, k=0.15). The number of HRT per patient was statistically higher in the progressing group (P=0.034).

• CONCLUSION: Agreement for detection of longitudinal changes between photography and HRT analysis was poor. One way to improve the chance of discovery of the progression could be increasing the number of HRT examinations.

• KEYWORDS: optic disc; juvenile glaucoma; Heidelberg Retina Tomography
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INTRODUCTION

In young persons glaucoma often results in more severe visual consequences than in adults, because of the life expectancy of the patients as well as delayed diagnosis[1]. The reasons for delayed diagnosis are usually the difficulty in getting useful visual field information in children (especially young children) and the great variability in the optic nerve appearance that often makes accurate distinction between glaucomatous and healthy optic nerve rather difficult. In the absence of a reliable visual field results ophthalmologists must rely on evaluation of structural changes on the optic disc, which, according to the reported results may precede the development of the reproducible perimetry defects by several years [2-4]. Suspected juvenile glaucoma cases could be monitored by comparison of optic disc photographs taken in regular time intervals. The photograph of the optical disc can show the first signs of glaucomatouse changes. However, disc photography assessment is subjective and this is what makes identification of glaucomatous change unreliable. This is why, along with monitoring the appearance of optical disc on the photograph, clinicians need imaging tehcnologies to detect changes in optic disc topography over time. Scanning laser ophthalmoscopy (Heidelberg Retina Tomograph, HRT) is an imaging technology that identifies glaucomatous change by using different analysing methods. For tracking glaucomatous progression by HRT some investigators

advocate topographic change analysis (TCA) whereas others suggested rim area linear regression line (RARL) against time[5-9].

The objective of this study was to evaluate agreement in identifying glaucomatous progression between HRT methods (TCA and RARL) and expert assessed optic disc changes using colour monoscopic photographs in young patients with suspected glaucoma.

SUBJECTS AND METHODS

Subjects This was a masked retrospective cohort study performed in the Clinic for Eye Diseases of the Clinical Center of Serbia. A retrospective chart review was carried out in patients younger than 35y admitted to the Clinic from March 2004 to October 2011. Each patient underwent a complete ocular examination by a glaucoma specialist including visual acuity, refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated stereoscopic examination of the optic disc with 78-D lens, fundus photography and HRT. Patients included in the study were glaucoma suspects with either glaucomatous-appearing optic disc and IOP under the 22 mm Hg or with healthy-appearing optic disc and IOP of 22 mm Hg or above. The criteria for determining the glaucomatous-appearing optic disc were assessed by the clinical impression of a glaucoma specialist. "Glaucomatous-appearing optic disc" must include one or more of the following: excavation, notching, focal or diffuse atrophy of neuroretinal rim area, vertical cup-disc ratio more than 0.6 or cup-disc asymmetry between fellow eyes greater than 0.2. Excavation was defined as undermining of the neuroretinal rim; notching was considered if it involved 2 clock hours; atrophy was defined as neuroretinal rim thinning involving 2 or more clock hours. Patients included in the study did not receive anti-glaucoma medications nor were operated. Inclusion criteria were: open angle on gonioscopy, spherical refraction within ±5.0 D and cylindrical correction within ±1.5 D, best-corrected visual acuity better than 0.8 (Snellen chart) and good image quality of photographs. Exclusion criteria were coexistence of any other ophthalmic pathology other than glaucoma and IOP above 30 mm Hg. Each patient had undergone an HRT examination (HRT Ⅱ, Heidelberg Engineering, GmbH, Dossenheim, Germany, version 2.02) using standard reference height of 320 μm. All eyes were examined at least three times with HRT with good-quality images and had to have at least two optic disc colour photographs. Only the best quality images were chosen for each optic disc. An image with adequate clarity was defined as one with good visibility of optic disc vessels and with sufficient detail for detecting optic cup margin. Optic disc photographs and HRT examinations were taken consecutively but only the good quality images were chosen for each optic disc. The first photograph was obtained closest to the first HRT examination and the final photograph was obtained closest to the last HRT examination.

Good-quality HRT images were those with image SD<25 μm, even image exposure and good centering. HRT images were obtained by the same experienced technician. Images having a honeycombed appearance were not included in the study. An operator outlined the optic disc margins while viewing photographs. The mean SD for all topographies included was 12.87±3.71. Optic disc photography was carried out with a Topcon fundus camera TRC-50VT (Topcon Instrument Corp. of America, Paramus, NJ, USA) upgraded with a Canon EOS 20 D digital camera. We analyzed progression of optic disc changes using colour photographs as well as HRT images.

All subjects received a detailed explanation about the study and signed an informed consent form in accordance with the principles embodied in the Declaration of Helsinki. In case the patient was a minor, the consent was obtained in addition to the consent of the minor's legal guardian. This study was approved by the Ethics Committee of the Clinical Center of Serbia within which the work was undertaken. The authors have no conflict of interest.

Methods

Progression on the colour photographs Progression of optic disc changes was defined as an observable increased narrowing in the optic disc rim between the first and the final photograph (Figure 1). In some cases progression was identified by the shifting of small vessels. Changes in the optic disc topography which were dependent on cardiac pulsation were not considered to be progression. The first and final photographs were assessed for glaucomatous progression by the two glaucoma specialists (NB, IS). The two observers independently evaluated the photographs in masked chronological order and were blinded to all patient information including HRT status. They had to indicate whether progression had occurred. They then re-examined the photographs together to reach a consensus as to whether the appearance of the optic disc had changed. Glaucomatous changes, as determined from the photographs by the two observers together, were used as the reference standard. Based on the reference standard, all eyes were classified into two groups: stable group and progressing group.

Progression on the Heidelberg Retina Tomograph Ⅱ Detection of change in HRT images was performed by the RARL (Figure 1) and the TCA (Figure 2). The TCA techique divides the image into a 64×64 superpixel array. Each superpixel consists of 4×4 pixels. Significant and reproducible changes in the topographic height of superpixels on the topography map are highlighted in red and in green. Red demonstrates significant depression of superpixels and green demonstrates significant elevation of superpixels compared to the baseline. For assessing glaucomatous progression of a cluster of superpixels, red super pixels were counted in the

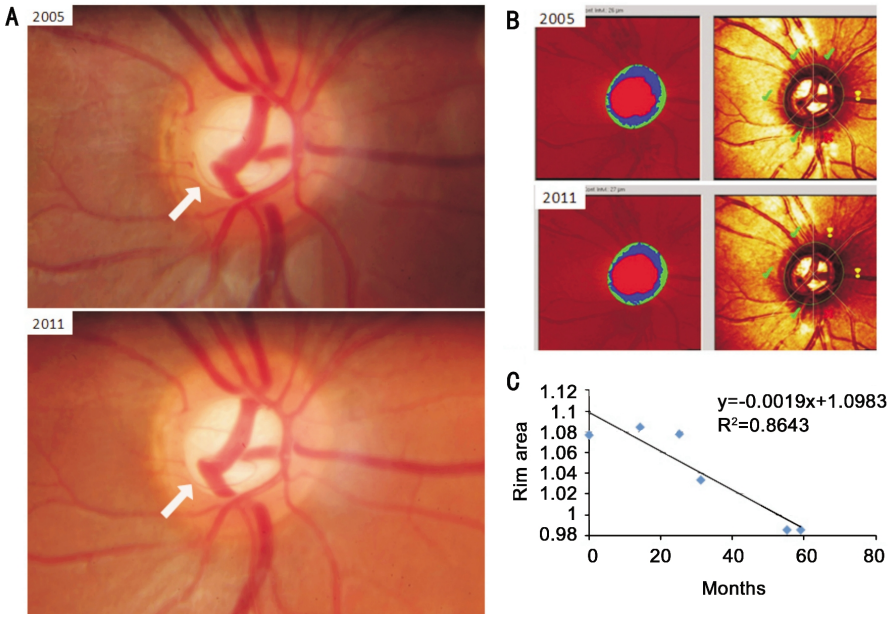

Figure 1 An example of the optic disc photographs and Heidelberg Retina Tomograph A: First and final optic disc photograph. Shifting of the blood vessel (marked with an arrow) suggests enlargement of the cup; B: HRT reflectivity image shows nasal enlargement; C: Rim are regression line (RARL) analysis demonstrates significant negative slope of the regression line.

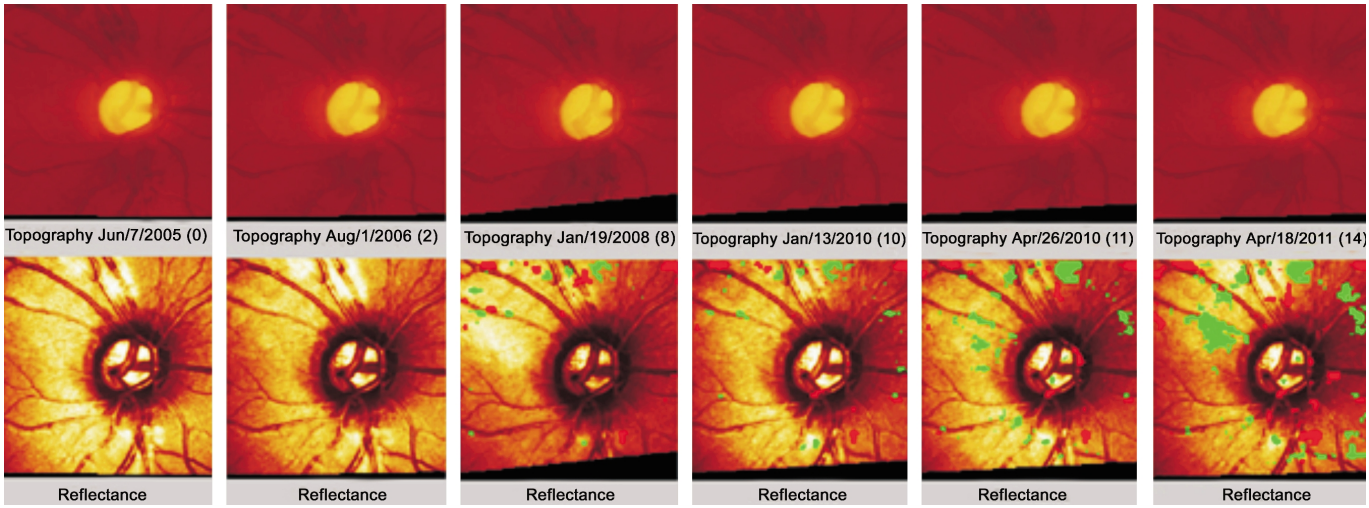

Figure 2 Heidelberg Retina Tomograph Topographic change analysis (TCA). TCA during the follow –up time does not demonstrate significant progression (less than 3 contiguous red super pixels are present).

largest contiguous cluster within the disc margins. Significant progression was identified when 3 or more super pixels (48 pixels) were present in the largest cluster. Any superpixels that fell on the vessels within the optic disc margins were discarded. Significance was defined as P value of 0.05. In addition, to determine and quantify the progression, a RARL for the whole rim area against time was performed. Progression was defined as present if a subject had a significant negative slope of the regression line (P<0.05).

Statistical Analysis Statistical tests Mann-Whitney U and χ^2 tests were used for comparison of the demographic and clinical characteristics between the stable and progressing groups differentiated on the basis of optic disc photographs consensus assessment. Significance was defined as P value of 0.05.

The kappa test was used to evaluate the agreement between progression by optic disc photographs and different HRT methods of analysis for glaucoma progression. A K value of less than 0.20 was considered a poor agreement, K=0.21-0.40 was considered a fair agreement, K=0.41-0.60 was considered a moderate agreement, K=0.61-0.80 was considered a good agreement and K=0.81-1.00 was considered a very good agreement. Statistical analysis was performed using SPSS, version 15.0 SPSS Inc., Chicago, USA.

RESULTS

The study included 31 patients (59 eyes) who met the inclusion criteria. There were 15 female and 16 male patients whose mean age at the last examination was 18.9y (SD 7.62, range 8-35y). The mean follow-up time between the first and the final photograph was 38.44mo (SD 13.52, range 12-63mo). The mean follow-up time between the first and the final HRT was 48.11mo (SD 15.53, range 22-72mo). The mean number

Table 1 Characteristics of stable and progressing groups based on optic disc photographs assessment $\bar{x} \pm s$, *n* (%)

Characteristics	Stable *n*=44	Progressing *n*=15	*P*
Age (a)	19.7±8.2	16.6±5.6	0.34
Male	10 (43)	6 (75)	0.22
Right eye	20 (46)	8 (53)	0.60
Visual acuity, Snellen chart	0.98±0.097 (0.5-1.0)	0.99±0.026 (0.6-1.0)	0.75
Refractive error, spherical equivalent, Diopter	-2.35±1.73 (-5.0-0)	-2.47±1.76 (-5.0 - 0)	0.85
Follow-up with photographs (mo)	37.6±12.4 (12-60)	39.7±16.3 (12-63)	0.56
Follow-up with HRT (mo)	46.3±15.2 (22-72)	53.4±10.5 (42-71)	0.089
Number of optic disc photographs per patient, median (range)	4 (2-7)	4 (2-8)	0.69
Number of HRT images per patient, median (range)	4 (3-7)	5 (3-7)	0.034
IOP (mm Hg)	21.7±2.6 (12-24)	23.0±6.6 (15-28)	0.74

of HRT images per patient was 4.20 (SD 1.17, range 3-7). The mean time difference between the first optic disc photographs and the first HRT examination was 7.25mo (SD 1.18) while the corresponding value between the final disc photographs and closest final HRT examination was 5.34mo (SD 1.23).

The stable and progressing group did not differ in age, gender, visual acuity, refractive error, follow-up time with photographs, follow-up time with HRT, mean number of optic disc photographs and mean IOP (Table 1). The number of HRT images per patient was statistically higher in the progressing group than in the stable group (Mann-Whitney test, P=0.034) (Table 1).

Table 2 presents the number and proportion of eyes classified as stable and progressing by means of photographs and two HRT methods. Table 2 suggests that TCA alone detected 10 out of 59 (17%) progressing eyes, whereas photographs alone as well as RARL alone detected 15 out of 59 (25%) progressing eyes. Figure 3 shows the Venn diagram demonstrating the level of consensus between the 3 methods of detecting glaucomatous progression: photographic assessment, HRT TCA and HRT RARL. Figure 3 shows that out of 15 eyes classified as progressing by consensus photographs disc assessment, only 7 eyes demonstrated progression by HRT in the following way: 3 eyes (20%) showed progression by photographs and RARL, 2 eyes (13.3%) showed progression by photographs and TCA and 2 eyes (13.3%) showed progression by photographs and both HRT methods, RARL and TCA. The remaining 8 eyes (53.3%) that were assessed as exhibiting glaucomatous change using the photograph reference standard, had no progressive change on HRT. Two eyes showed progressive changes only by both HRT methods, TCA and RARL.

Agreement between TCA and photography was obtained in 4 out of 15 eyes (26.3%) that were progressed by photography and in 38 out of 44 (86.4%) that were classified as stable by photography (Table 3). Agreement for progression/no progression between HRT TCA and photography was 71.19%, K=0.11. Agreement between RARL and photography was detected in 5 out of 15 eyes (30%) that were progressed by photography and in 34 out of 44 (77.3%) that were classified as stable by photography. Agreement for progression/no progression between HRT RARL and photography was 66.10%, K=0.15. Kappa values for agreement among photograph assessment and HRT methods of analysis for glaucoma progression indicate poor agreement between clinical judgment of optic disc photographs and progression identified by HRT (Table 3).

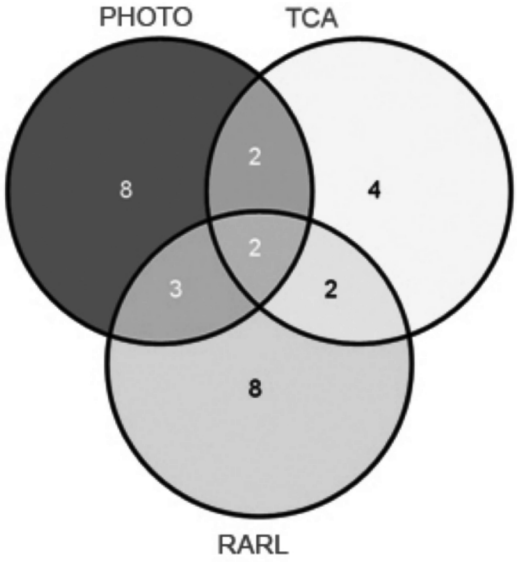

Figure 3 Venn diagram showing the number of eyes classified as progressing by 3 progressing strategies: photographs assessment, HRT topographic change analysis and HRT rim area regression line.

Table 2 Observation of change by means of photographs and Heidelberg Retina Tomograph methods *n*(%)

	Stable	Progressing	Total
PHOTO	44 (75)	15 (25)	59 (100)
HRT TCA	49 (83)	10 (17)	59 (100)
HRT RARL	44 (75)	15 (25)	59 (100)

DISCUSSION

In order to monitor the changes in optic disc apperance in suspected glaucoma cases it is advisable to take the photographs of the optic disc and to do optic disc imaging.

The evaluation of photographs is necessarily subjective, so great expectations are placed with HRT which represents a quantitative and more objective technique of meassuring

Table 3 Agreement between photography assessment and HRT methods of analysis for glaucoma progression *n*(%)

HRT	PHOTO stable *n*=44	PHOTO progressing *n*=15	*k*	SE
TCA	38 (86.4)	4 (26.3)	0.11	0.14
RARL	34 (77.3)	5(30)	0.15	0.14

K: Kappa value; SE: Standard error.

optic nerve head topography [10]. Studies have demonstrated that 4% to 19% of cup-disc estimates made by 2 different glaucoma specialists differed by 0.2 disc diameters or more [11-13]. Some studies suggest that HRT cup-disc ratio assessments are similar to disc photography [14,15], but other studies suggest that these differences are too large to be interchangeable in a clinic setting [16-18]. We evaluated a concordance between clinical judgment of sequential optic disc photography and the TCA and RARL method for detecting progression in HRT. Almost half of the eyes (8 eyes, 53.3%) that had progression on photographs assessment had no progressive change on HRT. Only 2 eyes (13.3%) showed progression by photography and both HRT methods, RARL and TCA. Agreement for detection of longitudinal changes between consensus photographs assessment and HRT analyses was generally poor (71.19% for progression between HRT TCA and photography and 66.10% for progression between HRT RARL and photography) (k=0.11 and 0.15 respectively). Our results are consistent with previous studies. When assessing the optic nerve for changes Vizzeri *et al* [19,20] reported poor correlation between TCA and stereo photography (82.3% agreement on 8 progressing eyes and 187 non-progressing eyes, k= 0.2). O'Leary *et al* [21] also reported poor correlation between HRT (TCA and RARL) and expert assessed stereophotograhs of the optic nerve for progression of glaucoma. Korkoutas *et al* [22] observed fair agreement between HRT Ⅱ TCA and clinical judgment of photographs for progression of glaucoma. They published concordance between the HRT TCA and optic disc stereophotographs assessment in 35 patients (65%); 16 patients (30%) showed progression on HRT Ⅱ only, while 3 patients (6%) showed progression on stereophotographs only. In previous reports authors postulated several reasons for disagreement between the photography and HRT analyses [21, 23-26]. Their assumption, among others, was that the reason for this discrepancy is the high variability of the HRT topographic measurements at the steep edges of the optic cup because the laser beam is reflected orthogonally and does not reach the detector of the HRT Ⅱ [24-26].

Optic disc morphology (steep edges of the optic cup) and corresponding orthogonal reflectivity of the laser beam might be the reasons for poor agreement in our teenage patients. As Jonas and Grundler [27] found, the patients with primary open angle glaucoma younger than 40y showed deeper and steeper optic disc cupping and concentric emaciation of the neuro-retinal rim when compared to the patients older than 40y. It is possible that deepening of the optic cup identified by HRT TCA could not be recognized on photographs because the location of the cup is not in the focal plane of the photographs.

Another possible reason for the difference may be that disc topography is dependent upon cardiac pulsation which causes changes in vessel caliber and vessel position. This can give the false impression of progression on HRT[28,29].

Other contributing factors for the disagreement between the photography and TCA could be the fact that until today the factors that define clinically significant change using TCA with the HRT have not been identified. Clinically significant change on the TCA is thought to be the presence of changed clusters of some minimum size [5,28]. In the present study, we considered confirmed change in the topographic height in two consecutive sets of follow-up images and the minimum number of progressed super pixels in the largest cluster size required for determining significant progression was 3 super pixels (48 pixels). On the other hand, Chauhan *et al*[30] considered confirmed changes in the topographic height in higher number of significant pixels in 3 consecutive sets of follow up images and concluded that agreement between clinical judgment of disc progression using optic disc photographs and HRT TCA was very good (13 of 16 cases, 81%).

One potential limitation of our study is the unknown effect of age on the optic disc measurement in teenagers. Since significant age-dependent changes occur in HRT parameters indicating increased ONH cupping during the 11y of follow-up in healthy persons [31]. Another limitation is the use of monoscopic photographs as opposed to stereo photographs. It is possible that a higher concordance might have been observed if these discs were assessed with stereopsis. The change in the level of lamina cribrosa due to variation of the level of IOP should not have significant effect on our results considering that none of the patients had IOP higher than 30 mm Hg and the average IOP during the first check-up was 21.7 ±2.6 mm Hg. Possible methodological limitation of the study is the fact that HRT and optic disc photographs were not taken on the same day. The mean difference in imaging between photographs and HRT was 5.34-7.25mo. This could be significant in that progression may have occurred within this relatively large window. In addition, in this study, a higher number of HRT images was performed in the group with progressing optic disc changes (an average of 5 HRT images) than in group with stable optic discs (an average of 4 HRT images). It is possible that a greater number of HRT images available for the detection of change may yield a better discrimination between "true change" or disease progression and measurement variability.

In conclusion, we revealed discrepancy between clinical assessment of photographs and HRT methods for detecting progression in glaucoma. We hypothesize that the increase in the number of HRT readings will enable reliable identification of glaucomatous progression.

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