Evaluation of Retinal nerve fiber layer thickness, mean deviation and visual field index in progressive glaucoma.

Sebastián A. Banegas,[1] Alfonso Antón, [2] Antonio Morilla,[2] Marco Bogado, [2] Eleonora M.Ayala[2], Agustín Fernandez-Guardiola[1] and Javier Moreno-Montañes[3]

1: INSTITUT OFTALMOLÒGIC QUIRÓN, BARCELONA, SPAIN 2: INSTITUT CATALÁ DE LA RETINA, UNIVERSIDAD INTERNACIONAL DE CATALUÑA, PARCC SALUT MAR, BARCELONA, SPAIN 3: CLÍNICA UNIVERSIDAD DE NAVARRA, PAMPLONA, SPAIN.

Brief Title: Retinal nerve fiber layer, mean deviation and visual field indices in progressive glaucoma.

Key words: *Retinal nerve fiber layer; mean deviation; visual field index; progressive glaucoma.*

Corresponding author: *S. Banegas-Argota. Institut Oftalmològic QUIRÓN . Av/Diagonal 632 . Barcelona 08017, Spain.*

Phone:+34 617254733 Fax: +34 932419102. E-mail: sebanegas@hotmail.com

PURPOSE. Determine and compare Retina Nerve Fiber Layer (RNFL) thickness, Mean deviation (MD) and Visual field index (VFI) in glaucoma cases with progression detected by Spectral Domain Optical Coherence Tomography (SD-OCT), Standard automated perimetry (SAP) and optic disc stereophotographs.

METHODS. The authors prospectively studied 246 eyes of 148 patients (97 glaucoma, 132 suspects and 17 healthy eyes). SAP fields, OCT images and optic disc stereophotographs were obtained every 6 to 12 months. Progression was determined in SAP and in OCT with Glaucoma Progression Analysis software, and also by masked assessment of stereophotographs series. Kruskal-Wallis Test was applied to evaluate differences between methods in RNFL thickness, visual field MD and VFI. The relationship between base-line classification and detection of glaucomatous progression by the different tests was assessed by Chi-Square statistic.

RESULTS. 99 eyes (40.2%) presented glaucomatous progression detected by at least one examination method. Progressing eyes detected only by OCT had higher mean RNFL thickness and mean VFI than progressing eyes detected only by VF or stereophotographs ($p<0.003$). Most progressive cases detected by OCT (68%) were initially classified at Baseline as suspects while most eyes with VF progression (61%) were initially classified as glaucoma. Initial classification was significantly related to the presence of progression by different test ($\chi 2(2)=9.643$ for VF event analysis and 7.290 for OCT event analysis ($p< .005$).

CONCLUSION. Different tests are more likely to detect progression in different clinical circumstances or stages of glaucoma, these should be taken in consideration when performing the difficult task of progression detection.

INTRODUCTION

Detection of glaucomatous progression is still one of the most difficult tasks in glaucoma management. While SAP and stereophotographs remain the gold standard for disease follow-up and identification of progression, none of them is ideal for that task (1). SAP depends on patient´s collaboration and is influenced by attention, cognitional, or behavior disorders. Moreover, SAP only detects functional defects after substantial structural damage has already occurred (2). Consequently, there is an important number of patients, glaucoma suspects or early glaucoma cases in whom identification of progression by visual fields is unlikely (3). On the other hand, assessment of optic disc´s appearance by series of stereo-photographs requires subjective interpretation and judgement agreement between expert graders is difficult to reach (4-5). Furthermore, stereophotos, as well as SAP, need long term follow-up to identify and confirm disease worsening (3). Finally, agreement in progression assessment among different functional and structural tests is only low (6- 8).

During last decade progression detection algorithms have been implemented into imaging devices. Glaucoma progression analysis (GPA) software for OCT allows identification and quantification of changes in RNFL and Optic nerve head over time and could be an useful tool to assess progression (9). OCT images do not require active patient participation and present excellent intra-visit and inter-visit reproducibility of peripapillary RNFL measurements (10-12).

However, the evidence-based knowledge on diagnostic accuracy and performance of GPA OCT´s algorithms throughout different stages of the disease (13) is lacking and there is still no consensus on how OCT-GPA results should be interpreted and applied in clinical decision making.

The present study is not meant to establish diagnostic accuracy, its purpose is to determine and compare Retina Nerve Fiber Layer (RNFL) thickness, Mean deviation (MD) and Visual field index (VFI) in patients with glaucomatous progression detected by SD-OCT GPA, SAP GPA and/or optic disc stereophotographs. The results could give key information about which test is more appropriate at different stages of the disease for detecting glaucoma progression.

METHODS

This is an observational cohort study. Two hundred and forty six eyes of 148 participants of a larger prospective study conducted at Institùt Català de la Retina (Barcelona, Spain) followed from June 2009 to July 2012, were chosen on the basis of number and quality of visual fields, SD-OCT images and stereophotos (see below). At baseline and follow-up visits medical history and full ophthalmic examination was performed and electronically recorded on a previously tailored data-entry glaucoma form. Ocular exams included visual acuity (Early Treatment Diabetic Retinophaty Study chart), manifest refraction, Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, pachymetry and dilated fundus evaluation using a 78D hand-held lens. Visual fields with 24-2 SITA standard strategy (Carl Zeiss Meditec, Jena, Germany) were performed every 6 months and optic disc stereo-photos with TRC-NW7SF fundus camera (Topcon, Tokio, Japan) were acquired every year. Images of optic disc and peripapilary region were obtained annually with Cirrus SD-OCT (Carl Zeiss Meditec, Jena, Germany) using the Optic Disc Cube 200x200 protocol.

Inclusion criteria required were at least 18 years of age, best corrected visual acuity 20/30 or better, spherical refractive error of +5 to -5 diopters, less than 3 diopters of cylinder and open angle; defined as ≥ 3 in the Shaffer´s classification. Subjects were

excluded if they had history of retina surgical or laser procedures, or any ocular or systemic disease that could cause optic disc, retinal abnormalities or visual field loss. Patients with severely depressed visual fields in which HFA GPA could not perform Event analysis were excluded. Patients with mild cataract could be included in the study. Acute and/or angle closure glaucoma were included.

Examinations

After several visits, the sample was divided into four groups based on base-line fields, optic disc appearance and ocular pressure: glaucoma, glaucoma suspect, ocular hypertension and normal. Glaucoma was considered if they had consistent glaucomatous visual field defects congruent with optic nerve damage. Glaucomatous visual field defect was defined as having three or more significant non-edge contiguous points outside the 95% normal limits in the pattern deviation plot (p <5%), with at least one at the $p<1\%$ level, or a glaucoma hemifield test result (GHT) outside normal limits in at least two consecutive exams. Optic nerve damage was defined by the presence of a localized notch, or rim thinning, or cup disc ratio >0.8, or a difference in this ratio between the two eyes >0.2, or a disc haemorrhage, or by the presence of retinal nerve fiber layer defects. Eyes classified as Glaucoma suspects had normal visual fields but glaucomatous optic disc appearance, patients with ocular hypertension (OHT) had high IOP (> 21 mmHg), normal fields and normal discs in 3 different consecutive examinations. Normal subjects had neither history nor pressure measurements over 21 mm hg in at least 3 different consecutive examinations, reliable normal visual fields (mean deviation and pattern standard deviation within 95% confidence limits and GHT result within normal limits in two consecutive exams) and normal fundus examination.

During follow-up time, each patient was treated at the discretion of the attending ophthalmologist. The study was conducted according to the tenets of the Declaration of Helsinski. All subjects gave informed consent, and the study was approved by the Ethics Committee of the Hospital Universitari Sagrat Cor.

Main outcome measures: Visual field indices (MD and VFI), OCT parameters (Average RNFL thickness) and the identification of change in optic disc photographs, fields and SD-OCT.

Identification of change in stereo-photos

Stereo-photos were assessed by two independent expert graders (MB and EA). Experts were blinded to patient´s history and to temporal sequence of the images. Baseline and follow-up photographs were compared using a stereoscopic viewer Screen-Vu (PS Mfg., Portland, OR 97202, USA). Experts were asked to look for rim thinning, increase in cup/disc ratio or disc asymmetry, disc haemorrhages or identification of new retinal nerve fiber defects or enlargement of pre-existing ones. Graders were required to get chronological sequence right in order to classify a progressing case. If consensus was not reached a third independent grader decided if progression was present.

Identification of change in VF

A minimum series of at least 5 reliable VF tests (fixation losses <30%, false-positive <20% and false -negative rates <30%) was required. GPA event and trend analysis implemented in Humphrey´s software were used to assess the presence of field changes over time. GPA event analysis compares follow-up exams to two baseline visual fields. Significant progression is considered if the change detected is greater than the deterioration expected to happen less than 5% of the time at the location in a stable

glaucoma patient ($p<0.05$). Both GPA Alert messages of *possible progression* (significant deterioration in 3 locations and 2 consecutive tests) or *likely progression* (significant deterioration in 3 locations and 3 consecutive tests) were classified as VF progression. The trend analysis of GPA calculates the rate of progression of visual field index (VFI) by a regression equation represented at the VFI plot. Significant negative slopes with $p<5\%$ were considered as visual field progression.

Identification of change in OCT

Change in SD-OCT images was analysed with SD-OCT GPA software version 5.0. Only scans with a minimum signal strength of 6, well centered and without artefacts were included. SD-OCT GPA also uses event and trend analyses. It compares retinal nerve fiber layer thickness in follow up images to that of two baseline images (event analysis) and determinates if a statistically significant change from baseline has occurred. The software also calculates the rate of change (trend analysis). The first two good quality scans were established as base line exams. A minimum of three exams are needed to generate a GPA printout. In follow-up scans, if a statistically significant change is detected once a yellow alert message of *possible progression* is indicated. When significant thinning is noted in two consecutive exams, a red *likely progression* message is indicated. Both alert messages, in any of the progression parameters, were considered as progression in SD-OCT. The following parameters were analysed by event analysis: RNFL Thickness Map progression (Thickness Map) and RNFL Thickness Profiles Progression (Thickness Profile). Trend analysis was performed for Average RNFL Thickness Progression (Average Thickness), Overall Thickness, Superior Thickness and Inferior Thickness.

Statistical analysis

Statistical analyses were performed with SPSS (ver. 20.0; SPSS Inc, Chicago, IL) and WINPEPI (PEPI-for-Windows 11.15). Descriptive statistics included means and SD for normally distributed variables and median, first quartile, and third quartile values for non-normally distributed variables. Distribution of numerical data was evaluated with the Shapiro-Wilk test. Student´s unpaired t-test (normally distributed data) or the Mann-Whitney test (non-normally distributed data) was used for comparisons between 2-groups, ANOVA (normally distributed data) or the Kruskal-Wallis test (non-normally distributed data) was used for comparisons between more than 2 groups. In all analyses a $p<0.05$ was considered as statistically significant.

A cross-tabulation table showing number of progressing eyes in normal, ocular hypertension, glaucoma suspects and glaucoma cases detected by each diagnostic algorithm was plotted.

Mean RNFL thickness, MD and VFI for each test algorithm in progressing and non-progressing cases and specificity values using “normal” cases as controls are presented in table 3.

The relation between base-line classification and the detection of glaucomatous progression by different tests was assessed by Pearson Chi-Square and Cramer's V test.

RESULTS

Two hundred and forty-six eyes of 148 patients (97 glaucoma, 63 suspects, 69 ocular hypertension and 17 healthy eyes) were enrolled and followed from June 2009 to July 2012 (mean 31.8 +/- 6 months, range 20-37 months). Patient´s demographic and clinical characteristics are summarized at table 1.

Frequency tables were built with the number of progressing cases detected by one, two or three methods and by different diagnostic algorithms from each test (Table 2). Ninety-nine eyes (40.2%) presented glaucomatous progression detected by an examination method. Eighty-four cases were detected by only one diagnostic test, 12 by two tests and 3 cases by all 3 methods (table 2).

More than half of progressing eyes detected by only one method (63%, 53/84) were identified with OCT event and/or trend algorithms. Twenty-seven progressing cases were detected only by OCT event analysis, 7 were identified only by OCT trend analysis and in 19 cases both strategies identified significant change (table 2).

Significant differences in terms of mean RNFL thickness, visual field MD and VFI between progressing and non- progressing eyes were present using both VF´s algorithms ($p<0,03$). When Stereo-photos were utilized to detect abnormal change significant differences between progressing and no-progressing cases were found only in mean VFI ($p=0.013$). On the other hand, only OCT´s trend analysis parameters, *Average and Superior thickness* showed statistical differences between cases in terms of mean RNFL thickness. The 3 techniques obtained good outcomes in terms of specificity (82%-100%), (Table 3).

We observed that mean RNFL thickness for non-progressing cases in all 3 methods range from 81 to 82 microns, interestingly, stereo-photographs and VF´s means for progressive cases are bellow this range, <82µm, while all OCT´s parameters means for progressive cases are above 82 µm. The same situation occurs when analysing the other 2 variables, MD and VFI means. Non-progressing eye´s mean MD and VFI range from -1.7 to -2,5dB and from 93 to 95% respectively for all 3 methods. Photos and SAP´s mean MD and VF for progressing eyes are bellow these intervals

while OCT´s progressive cases means are above. Therefore, we could consider these ranges as limits that divide scenarios or proper setting for glaucomatous progression identification with different diagnostic modalities (table 3).

Table 4 indicates mean**,** SD, medians, first and third quartiles values of average RNFL thickness, MD, VFI, pachymetry and age in progressing cases for each diagnostic algorithm. Progressing eyes detected only by OCT trend or event analysis had higher mean RNFL thickness, 88.1 +/- 16.4 and 82.3 +/- 9.2 microns respectively, than progressing eyes detected only by VF´s trend, VF event analysis or stereophotographs, 76.8(+/-17.2), 72.5(+/-12.12) and 69.6 micras (+/-8.9) respectively ($p<0,03$). Statistically significant differences between test were also found in mean VFI ($p<0.006$) but not in mean MD ($p=0.08$), age ($p=0.48$) nor pachymetry ($p=0.15$), (Table 5).

In our study, 53 eyes were only identified as progressors by OCT GPA algorithms (54% of all progressing cases). These cases presented high mean RNFL thickness (>82µm), high MD (>-2dB) and VFI between 93% and 96% values (table 4). Most of these cases were classified at base-line as OHT or glaucoma suspects, not presenting previous glaucomatous VF defects. The fact of having been classified as OHT or suspects of the disease affected the chance of finding progression by an OCT event algorithm ($p=0.043$) (table 5). These data reaffirm the statement that OCT is a useful tool for detecting and monitoring progression in pre-perimetric patients at early stages of the disease. Sixty-three percent of progressing cases detected by OCT event analysis were classified at baseline as OHT (26%) or as glaucoma suspect (37%) and 35% as glaucoma, while most of progressing cases identified by visual field changes were glaucoma patients at baseline, (VF event analysis 69% and VF trend 50%). Baseline classification (normal, OHT, glaucoma suspects and glaucoma cases) was significantly

related to presence of progression detection ($\chi 2(2) = 10.64$ for VF event analysis and 8.16 for OCT event analysis $p < .005$), both with moderate relationship (Cramer´s V = 0.328 and 0.287 respectively) Table 5.

DISCUSSION

Diagnosing glaucomatous progression throughout the different stages of the disease is a challenging but essential part in glaucoma management. Progression´s detection has an important clinical relevance, confirming conversion to glaucoma in suspect cases, helping to estimate prognosis and having significant influence over management decisions.

The present study intends to help clinicians identifying progression by adding knowledge about the characteristics of glaucoma patients that are associated or may favor the detection of worsening with each of the three most frequently used test: optic disc photos, SD-OCT and VF.

As was enunciated in previous studies, lack of agreement among tests to identify progression in glaucoma may be due to temporal frames differences in the appearance of structural and functional changes, or to differences in the capability of instruments and algorithms to detect those changes (7-8, 14-18). Our results sustain this fact (table 2). Most eyes with abnormal change were identified by only one diagnostic test and only in 15 cases (15%) two tests concured detecting progression. Moreover, total agreement among all 3 tests was only found in 3 cases.

Several studies suggest that test performance for detecting progression could vary throughout the different stages of the disease. Subtle glaucomatous progression at early stages is possibly more difficult to detect on disc photos or VF but could be identified by measuring RNFL thickness. Medeiros et al. detected early damage with

scanning laser polarimetry Nerve Fiber Index (NFI) in a cohort of 40 eyes suspected of having glaucoma based on optic disc assessment but with no VF loss, and obtained a 83% sensitivity value(3).

On the contrary, changes in moderate and advanced stages of glaucoma are better identified by VF or stereophotographs (17, 19-23). A previous cohort study performed by Vizzeri et al, showed that progressing eyes according to SAP´s GPA and/or stereo-photographs had more advanced disease at baseline, compared to cases that progressed only by the Topographic Change Analysis of the Confocal Scanning Laser Tomograph (8). Another study from Medeiros et al, including 98 eyes with diagnosis of glaucoma and 246 considered glaucoma suspects, showed that eyes that progressed by photos or/and SAP had significantly thinner RNFL at baseline than eyes that did not show progression (17). All these results are in agreement with our findings showing that eyes progressed by conventional methods had more severe disease in terms of RNFL thickness means and VFI lost ($P<0.05$).

The results from the study indicate optimal settings for detecting progression with stereophotographs as cases within 61-78 microns of mean RNFL thickness (95% IC.), with mean MD between -9.5 and 0,9dB (95% IC.) and VFI boundaries between 73% and 100% (95% IC) (table 4). Half of the progressing eyes detected by this method were classified at baseline as glaucoma cases, and the other half as glaucoma suspects (Pearson Chi-Square $p= 0.187$).

In the worst glaucoma cases, with thinnest mean RNFL thickness, and lowest mean MD and VFI, SAP had the best performance for detecting progression. Eyes in which progression was detected presented mean average RNFL thickness < 76 micras, MD <-3dB and mean VFI <86%. The presence of an abnormal VF at baseline was

significantly related to presence of progression detection by VF event strategy (p=0.043). This relationship between VF defect and progression detection was not found with photos or with OCT (table 5). These results denote the capability of VF test to identify and assess changes in moderate and advanced stages of the disease.

Diagnostic tests performed significantly better detecting damage in subjects with more severe disease. This fact has been described and reported for almost all diagnostic tests and recently confirmed also for the latest versions and parameters of SD-OCT.

In a recently study, Rao et al. found that the diagnostic accuracies of the OCT RTVue scanning protocols for glaucoma detection (ONH, RNFL and macular parameters) were significantly influenced by disease severity, graded using the Visual Field Index (VFI). For a VFI of 99%, areas under the ROC curve for Rim area, average RNFL thickness and Ganglion Cell-root mean square were 0.693, 0,799 and 0,779 respectively, while for a VFI of 70% all scanning areas increased to 0.828, 0.985 and 0.992 respectively (23). Leite et al. in a previous study, also taking into account disease severity, reported Cirrus OCT´s performance in detecting eyes with glaucoma. Average RNFL parameter´s AUC increased the area from 0.822 to 0.962 when reducing VFI to 70% (24).

However, when the task is progression detection, the relation between degree of damage and the sensitivity of OCT may not be the same as when the task is detecting the disease. Leung et al found with Stratus OCT, that the rate of change in RNFL thickness was related to the baseline RNFL thickness. A greater baseline RNFL measurement was associated with an increased rate of RNFL reduction (19).

The fact that both VF´s algorithms obtained significant differences between progressing eyes and non- progressing eyes in mean RNFL thickness, MD and VFI,

while OCT only presented statistical differences in mean RNFL thickness in only two analysis parameters (table 3), is probably a consequence of the differences in the disease´s severity of the detected cases. OCT´s progressing eyes RNFL thickness and particularly visual function were not too different from that of normal patients. On the contrary, the subjects with progressive glaucoma detected by VF showed more advanced damage and marked differences with cases classified as non-progressive.

Sung et al, obtained similar outcomes following with SAP and OCT 88 suspected glaucomatous eyes (13 HTO and 75 with glaucomatous optic disc changes) for a period of 4 years. Non-converters to glaucoma group had a base-line mean MD (SD) of -1.6 (1.8)dB and a baseline mean (SD) RNFL thickness of 92.2 µm (10.5), while the glaucoma converters group showed mean (SD) MD of -2.7dB and mean (SD) RNFL thickness of 86.3 µ (8.8) (25). The smaller mean RNFL thickness among progressors in our study was probably caused by the inclusion of glaucoma cases, with thinner RNFL, that were not included in Sung´s study.

Our study has certain limitations. Firstly, the absence of an ideal gold standard test to define progression and the lack of agreement between conventional tests make all analysis less precise. This day a day practice situation forces us to combine different diagnostic tests (structural and functional) and different algorithms (event and trend analysis). Secondly, the follow-up period could be considered slightly short, but the relatively recent GPA algorithm´s incorporation to the OCT device and the slowly progressive nature of glaucoma, limit follow-up time. However, 99 cases were identified as progressive glaucoma and tests were able to obtained results with statistical significance. Finally, differences in prevalence of progression detection between tests limits statistical analysis, but this drawback was counterbalanced applying non-parametrics statistic as independent-samples Kruskal-Wallis test.

In summary, this study resulted in several findings that may improve patient management and our understanding of the complex relation between changes in structure and changes in visual function as glaucoma evolves. First, and confirming previous studies, there is little agreement among tests and algorithms when identifying progressing eyes. Second, there are statistically differences in RNFL thickness, MD and VFI among progressing and non-progressing cases, but these differences are not homogeneous among the different tests, or even different algorithms of the same test.

The results suggest that, in clinical practice, OCT is more likely to detect progression in pre-perimetric settings and early glaucoma cases with Average RNFL thickness >83μ, MD >-2.5dB and VFI >93%, Whereas VF and stereophotographs capabilities to detect progression would be greater identifying disease worsening at advanced stages. These findings should be taken in consideration when assessing glaucomatous progression.

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