Detection of Visual Field Loss Progression in Glaucoma: An Overview and Food for Thought

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Author’s contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

The damage to the visual field is the main outcome of glaucoma. Basically, there are two different approaches to establish the rate of the functional loss in this clinical condition: event-based analysis and trend-based analysis. The event-based analysis, that relies on the occurrence of pre-established events to detect the progression of the visual field damage, cannot quantify the decay rate of sensitivity. In turn, the trend-based analysis, that aims to measure the rate of progression according to linear regression models, requires a long follow-up. Despite considerable effort, there is still no consensus on the optimal procedure, and a gold standard is still missing. This paper provides a quick overview of the topic as a tribute to the researchers engaged in this field.

Keywords: Glaucoma; visual field; perimetry; progression; AGIS; CTGS; GSS; point-wise regression.

1. INTRODUCTION

The damage to the visual field is the main outcome of glaucoma. Since the goal of the treatment is preventing the deterioration of the quality of life, detecting a change of the visual function on a time scale basis is paramount for monitoring the effectiveness of the therapy. As a matter of fact, De Moraes and colleagues demonstrated that a 30% decrease in the rate of visual field progression in a time interval 12–18 months long will have a significant effect on the future quality of life of the patient [1]. Nevertheless, the assessment of this parameter

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is hindered by variables like fluctuation of light sensibility, psychophysical state, presence of other ophthalmological conditions which can mask the glaucomatous perimetric features and, last but not least, the lack of a gold standard among the different strategies advanced so far. The ideal technique to identify the progression of the visual field damage should be sensitive, specific, robust against noise, and the follow-up needed to detect functional changes should be as short as possible.

2. FUNCTIONAL LOSS AND RATE OF FUNCTIONAL LOSS

Among all the techniques devised to assess the characteristics of the functional loss in glaucoma, we will consider the following:

- The AGIS Scoring System [2]. In the AGIS Scoring System, the 24-2 Total Deviation map of the Humphrey Visual Field Analyzer is divided into three areas: nasal, superior, and inferior, and a score is assigned to each perimetric defect. The occurrence of a defect and its relative score is based on operative definitions: to be considered as depressed, the sensibility in a locus must be reduced by at least 5 or 9 dB (depending on its position). Therefore:

  - a nasal defect is defined as a cluster of three or more depressed loci in the nasal area;
  - a nasal step is made of one point or a cluster of 3-5 points on the upper or lower side of the horizontal meridian without a correspondent defect on the opposite side.

In both cases the assigned score is 1. The score is higher (score=2) if at least 4 points in the nasal area are depressed by at least 12 dB or in presence of focal losses made of 6 or more contiguous points: the higher the number of points of the loss, the higher the assigned score. Besides, scoring is weighted by the depth of the loss. The grading is arranged so that a normal visual field scores 0 and a visual field at the final stage of the disease scores 20. The AGIS system defines as “progressed” visual fields with a score increased by at least 4 points in three consecutive examinations [3]. According to the score, the visual field can be classified into 5 stages (1: normal, 2: mild damage, 3: moderate damage, 4: severe damage, 5: end-stage).

- The CIGTS Scoring System [4]. The CIGTS Scoring System considers the probability of the depression rather than on its depth. The cut-off for significance is set at p≤ .05 and a score higher than zero is assigned to each point in a defective area made of three or more neighboring deviated loci. The score ranges from 1 to 4 based on the probability level of the deviated loci (p≤ .05: score 1, p≤ .02: score 2, p≤ .01: score 3, p≤ .005: score 4). According to this procedure, every locus is assigned a 0-4 score, and the final score of the visual field is the sum of the scores computed in each of the 52 tested loci (program 24-2, Humphrey). The final score is divided by 10.4. The CITGS system defines “progressed” a visual field with a score increased by at least 3 in three consecutive examinations.

- The Glaucoma Change Probability Analysis (GCPA [5]). The GCPA is an event-based method aimed to detect the probability of a visual field change by comparing the sensibility at each locus of the actual exam (24-2 Total Deviation map) with that of the previous one or two. The probability that each locus has changed more than expected by the fluctuation of sensibility is computed as a p-value ≤ .05. The probability of progression is defined as the presence of three or more loci (not necessarily contiguous) with a probability of change ≥ 95% as compared to the two previous exams.

- Point-wise linear regression analysis. This statistical technique performs a regression analysis in a series of consecutive visual fields for each correspondent locus. Progression of the damage in a locus is detected if the correspondent regression slope is statistically significant (p<.01) and the loss of sensibility is at least 1 dB/ year. It is assumed that a visual field has progressed if a change is found and confirmed in at least two or three points in three or more consecutive visual fields [6,7]. Point-wise linear regression has the advantage to measure the rate of progression, and the rate of progression is stated to be the main predictive factor for further progression [8].

- The Glaucoma Staging System (GSS) and the enhanced Glaucoma Staging System (GSS2) is a procedure that plots on an x,y diagram the Humphrey mean deviation and
corrected pattern standard deviation (or the mean defect and the corrected loss variance in the Octopus perimeter). The procedure has been devised based on 500 visual field examinations obtained from 471 glaucomatous patients at different stages of severity. The GSS classifies visual fields into 6 stages according to the severity of the perimetric loss and into 3 classes according to the type of visual field defect (localized, generalized, mixed: [9]. In the enhanced glaucoma Staging System (GSS 2), an additional stage “borderline” is added, and mathematic formulas are provided to allow the integration of the system in a PC software [10]. The correlation of the GSS2 with the AGIS categories and the AGIS score was consistent (Spearman r: 0.89 and 0.93, respectively) [10], and the agreement of the GSS and other classification procedures evaluated in a retrospective analysis of 610 Octopus visual fields proved to be good; when found (11% of the cases), the lack of agreement was related to high short-term fluctuation [11]. Recently, is has been argued that the GSS2 based on 24-2 (or 30-2) visual fields underestimates the severity of the disease in the presence of macular damage because it does not adequately assess the macular function [12].

The effectiveness of these methods in analyzing the glaucomatous visual field progression has been compared (see for example [7,13,14]. Vesti and colleagues addressed this issue by performing a simulation using a series of at least 8 exams encompassing 7 years obtained from 76 glaucomatous patients [7]. Based on the first and last examination, 6-months interim maps (14 in total) were generated using a linear interpolation of the point-wise threshold values. The interpolation was adjusted by three different levels of short-term fluctuation (SF: 0 dB, 1 dB, 2 dB) and two levels of long term fluctuation (LF: 0 dB, 1 dB), expressed as Gaussian distributions of a probability density function. Three different levels of variability were tested in the model (no variability: SF and LF=0 dB, low variability: SF and LF= 1 dB, high variability: SF=2 dB, LF=1 dB). The authors estimated for each method the follow-up time required to detect the progression of the functional loss, the efficacy of its identification, and specificity.

In the AGIS system:
- follow-up required to detect progression: 5.1-5.3 years;
- detection of progression: from 18% in no-variability conditions to 8% in high variability conditions;
- specificity: ~100%.

In the CIGTS method:
- follow-up required to detect progression: shorter than AGIS;
- detection of progression: better than AGIS but worse than GCPA and point-wise linear regression analysis;
- specificity: 95-100%.

In the GCPA method:
- follow-up required to detect progression: shorter than the AGIS and the CIGS (in this case in conditions of high variability);
- detection of progression: up to 62% in no-variability conditions and up to 86% in high variability conditions (i.e. higher than AGIS and CIGTS);
- specificity: 95% in the moderate variability condition, 68%-75% in the high variability condition.

In the point-wise linear regression analysis:
- follow-up required to detect progression: 5.5 years;
- detection of progression: 72-84% in no-variability conditions, slightly less in the variability conditions;
- specificity: 82-100%.

So, according to the adopted criteria, the AGIS was the most conservative whereas the CIGS method was more effective and required a shorter follow-up [7,15]. The GPCA system and the point-wise linear regression analysis identified the progression in a higher percentage of cases compared to AGIS and CIGTS, suggesting a high sensitivity to small changes. However, the GPCA seems more vulnerable to noise in the advanced stages, revealing in these cases a high rate of false progressions [16-18]. In a comparative study dating back 2012, the agreement between GSS2 and AGIS was substantial (K=0.778), but the GSS2 staged the defective visual fields more severely compared to AGIS [19]. On the one hand, the main drawback of the linear regression analysis is the follow-up required to detect the visual field progression. On the other hand, the event-based methods are not as accurate as the regression analysis techniques to measure the rate of change. In the clinical practice, linear regression analysis is
usually computed from the global index Mean Deviation or Mean Defect and provides the rate of the overall change of sensibility in the visual field. However, it is worthwhile recalling that the sensitivity of the linear regression procedures (be they point-wise or not) is not suitable for the detection of progression at the early stages of damage [20].

3. THE GLAUCOMA PROGRESSION INDEX (GPI)

Generally, linear regression analysis and the other systems for detecting the glaucomatous functional progression rely on the dB deviation from normative data or on the probability estimate that the loss has occurred in a given locus of the visual field. These methods are biased by concomitant events, like cataract or other media opacities, which indeed are frequent in the elderly glaucomatosus population. In turn, the progression of the glaucomatous damage can be masked from the increased levels of retinal illuminance after cataract surgery [21-23]. To minimize these sources of noise, the Glaucoma Progression Index (GPI) or Visual Field Index (VFI), has been devised by Bengtsson and Heijl [24]. These indices, expressed as percentage scores, are obtained by weighted point-wise regression analysis. The GPI is computed from the pattern deviation probability map: the sensitivity in each normal point of the map is scored 100%, whereas points of absolute defect are scored 0%. Points with relative defects at p<.05 level of significance are scored as the percent ratio of their threshold deviation (total deviation) and the expected normal age-corrected threshold according to the equation:

\[
100 - \left( \frac{\text{threshold deviation}}{\text{normal threshold}} \right) \times 100.
\]

This way, the smaller is the threshold deviation in that locus, the closer is the score to 100%.

In addition, the score in every point is weighted according to the salience of the central region compared to the peripheral ones by a factor that accounts for the cortical magnification of the visual field, i.e. for the different ganglion cells density at each eccentricity. The weighed GPI score makes the same amount of functional loss worse if the involved regions of the map are central rather than peripheral. The Glaucoma Progression Index, thereby, is computed as the mean of the weighted score in every locus of the perimetric map.

When in a set of consecutive visual fields the rate of progression expressed as MD (Mean Deviation or Mean Defect) in percent and as GPI is compared, results will be different, depending on the absence or presence of noise (for example cataract). With no noise (i.e.pseudophakic eyes), the rate of progression is almost identical for the two parameters (2.6%/year and 2.7% year respectively [24]. However, in presence of noise (cataract) the rate of MD progression is faster (MD: 3.6%/year, GPI: 2.1%year), and, after cataract surgery, the GPI shows less improvement compared to the MD [24]. In these two cases, the scattering of the observations across the regression line referred to the GPI was smaller and the confidence interval was narrower, suggesting that the regression analysis based on the GPI is more robust than that provided by the MD.

A main drawback of the GPI is that in the advanced stages of the disease the diffuse component of the functional damage tends to increase and becomes predominant over the localized defects [25]. In these cases the index underestimates the progression rate. In effect, the specificity of the pattern deviation maps decreases in compromised visual fields. Setting the average sensitivity of the map to the 85th percentile most sensitive point of the normative values allows masking a diffuse depression due to sources other than glaucoma (noise) so that the fascicular defects are enhanced.

As the Mean Deviation index (or Mean Defect) increases, the number of statistically depressed points in the pattern deviation probability shows a non-monotonic distribution, it reaches a peak at -20 dB, then decreases. The peak is taken by Bengtsson & Heijl as the cut-off level of the global MD beyond which the GPI is no longer reliable. So, the rate of progression in visual fields with an MD worse than -20 dB should be assessed by using the total deviation rather than the pattern deviation maps [24].

More recently, other methods to detect and quantify the visual field progression have been introduced. De Moraes and associates [26] developed a parameter modeled on the visual field index, they called central field index (CFI). The CFI is calculated scoring the sensitivities at test points (using the 10-2 strategy) as percentages, like the VFI; in addition, each point is weighted based on the cortical magnification. Their procedure proved to be effective in monitoring the perimetric evolution of central and
paracentral defects of glaucomatous patients and did not suffer from the biasing effect of media opacities. Zhu and colleagues [27] developed the ANSWERS (Analysis with Non-Stationary Weibull Error Regression and Spatial Enhancement), a method that considers the increasing rate of variability as glaucoma progresses and takes account of the spatial correlation among different loci in the visual field. ANSWERS is reported to be more sensitive in detecting VF progression compared to the linear regression of the Mean Deviation and the pointwise linear regression analysis. Warren and colleagues [28] developed a statistical model to compute the probability of visual field progression. The model takes into account rates of change in sensitivity at each locus of the visual field, where the contribution of each locus is related to the contributions at nearby locations through the use of a spatially referenced prior distribution. The authors, for example, determined that in the nasal regions of the optic disc the impact of decreasing sensitivities over time on the probability of diagnosed progression is small. On the contrary, it is greater in the temporal, regions.

4. CONVERSION FROM OCULAR HYPERTENSION TO GLAUCOMA AND RATE OF PROGRESSION

It is well known that IOP reduction minimizes the switch from ocular hypertension to glaucoma [29], and it slows down the progression of the functional loss in glaucomatous patients [30,31]. An additional independent risk factor for glaucoma conversion in patients with ocular hypertension is pseudoexfoliation syndrome: in this case the risk is double compared to IOP, age, and gender-matched patients without pseudoexfoliation [32].

The question now is: what promotes the functional loss progression in glaucoma?

The Canadian Glaucoma Study (CGS) identified four main risk factors, namely: high average IOP, age, increased anticardiolipin antibodies (ACA) at baseline, and female sex. The survey evaluated if these factors, aside from increasing the risk of functional damage, affect the rate of the damage progression as well [33,34].

The results confirmed the negative effect of age and especially of abnormal levels of ACA (ACA+) on the visual field progression: the decay was 4 times more likely in the ACA+ patients and the rate of progression was faster compared to the ACA- patients (-0.57 dB/year vs. -0.03 dB/year [33]. The subjects who showed significant progression had a mean loss of -0.54 dB/y vs 0.06 dB/y of stable patients. In the first case, a further 20% IOP lowering at the endpoint reduced the progression rate by 0.25 dB/year (from -0.36 dB/year to -0.11 dB/year).

More recently, age, peak IOP, pseudoexfoliative glaucoma, and baseline MD have been confirmed as risk factors for rapid visual field decay by Kim and colleagues [35]. In addition, low corneal hysteresis and reduced corneal thickness facilitate the visual field progression in glaucomatous subjects with well-controlled intraocular pressure [36].

A more aggressive therapeutical intervention is required in the case of patients with papillary hemorrhages. Medeiros and associates [37] showed that the overall rate of VFI progression is significantly worse in eyes with papillary hemorrhages (-0.88%/years vs -0.38%/years in eyes with no papillary hemorrhages).

Additional risk factors for the rate of progression are:

- the initial rate of visual field change so that a faster initial progression is a predictive factor for further, fast progression.
- the retrobulbar blood flow: in a study by Yamazi and Drance, patients with NTG showing a negative perimetric trend had increased arteriolar (central retinal artery and short ciliary posterior arteries) resistance and decreased blood flow velocity compared to stable NTG subjects. Instead, no difference was found in cases with open-angle glaucoma [38].

How many perimetric tests should be administered to the patient per year? Using a simulation method, Anderson and colleagues [39] showed that the predictive values of annual visual fields at 2 years were slightly worse than those obtained using six visual fields. In other words, reduced test frequency (one per year) does not substantially alter the prediction of progression computed with a higher (namely six) numbers of examinations at 2 years.

It remains that the optimal number of tests depends on the previously estimated rate of progression and the intra-subject variability: the slower the first and the higher the second, the
higher the frequency of the examinations required during the follow-up. Chauhan and associates [40] reckoned the minimum number of examinations required to detect a perimetric progression. His estimates varied from 5 exams for a rapid progression and low threshold variability up to 13 examinations in patients with moderate progression and moderate threshold variability. This rule of thumb must be modulated as a function of the type and localization of the perimetric defects (for example central scotomas threatening the fixation point should be checked more often).

Since the progression in glaucoma can be non-linear or episodic [41-43], it is worth considering whether a linear model fits well enough with this parameter. Acceleration (i.e. a deviation from linearity), indeed, is expected for advanced functional losses and in elderly patients: in fact, advanced loss and age are two main factors associated to increased risk of progression [8, 44-48]: so, a non-linear model might account better for the functional loss at the advanced stages of the disease. Likewise, the progression of the perimetric defect starting from normal visual fields is expected to be less linear compared to the consolidated loss condition [20]. Despite these considerations, the prediction based on linear regression is overall accurate, so that it is considered the most suitable paradigm [49-53].

Despite the consistent inter-patient variability, different rates of loss in different forms of glaucoma have been outlined: in particular, the mean rate of progression in subjects with normal-tension glaucoma is 0.43 dB/y [54], whereas, according to the Early Manifest Glaucoma Trial, in patients with open-angle glaucoma is on average 0.36 dB/y; for each 1 mmHg of IOP reduction, the rate of progression decreases by about 10%. However, it can decrease till to 1.31 dB/year in patients with high IOPs [55], and it can reach up to 3 dB/year in pseudoexfoliation syndrome [56].

5. FUNCTIONAL VS. STRUCTURAL: WHICH IS THE BEST PREDICTOR?

Once the importance of investigating the progression of the functional loss in glaucoma is ascertained, the question arises whether perimetric progression is sensitive enough to justify therapeutic changes.

The comparison of functional (i.e. visual field measurements) vs structural (retinal fiber layer thickness or rim area of the optic disc) loss demonstrated a worsening of the structural indices in the early stages of the disease (i.e. when the visual field is still normal or quasi-normal); in turn, in the advanced functional stages (severe deterioration of the visual field), a small progression of the structural loss is observable [57]. So, the morphological evaluation (optic disc changes) seems more sensitive than the functional (perimetric) assessment in the initial stages of the disease, whereas the opposite takes place at the advanced stages.

This structural/functional dissociation has been reported in several studies [58,59] and makes the assessment of the optic disc integrity as important as the perimetric follow-up to establish whether a progression of the disease has occurred. However, as maintained by Heijl [56] a statistically significant worsening of a structural parameter is clinically uncertain since the structural measurements cannot be translated to the visual function domain. Clinical management requires the present visual field and the rate of progression of visual field defects. Evidently, the detection of glaucomatous progression is improved by combining functional and structural outcomes. Recently Medeiros and colleagues have proposed a new technique able to incorporate functional and structural changes through a Bayesian hierarchical model [60].

6. CONCLUSION

In conclusion, the assessment and characterization of the progression of functional damage is a fundamental variable in the management of patients suffering from glaucoma. The fluctuation of sensitivity, the frequent association of biasing clinical conditions like media opacity or diabetic retinopathy, and, last but not least, the difficulty to test patients frequently and regularly makes this goal difficult to achieve. The chronic condition of this disease and the ever-increasing life expectancy make it mandatory to detect early changes and to predict the functional outcome over the years: this, in order to minimize the effective therapeutic regimen and avoid the deterioration of the quality of life. In everyday care the availability of reliable parameters to monitoring visual field changes are fundamental tools to adjust the therapy of glaucomatous patients. Even if the procedures developed so far yield important elements to customize the treatment with even higher precision, a gold standard is still missing. Probably the solution relies on an algorithm that
encompasses the advantages of each method recalled in this paper, and, at the same time, suitable to be easily integrated into the most common perimetric software. The morphological datum undoubtedly is an additional, precious source of information that should be introduced in the equation. Further research to obtain a standardized, user-friendly, reproducible, and PC compatible algorithm, therefore, is required.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

19. Ng M, Sample PA, Pascual JP, Zangwill LM, Girkin CA, Liebmann JM, Weinreb RN,


47. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology. 2007;92:569-73.

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