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Linear regression analysis of the cumulative defect curve by sectors and other criteria of glaucomatous visual field progression

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PURPOSE. *To analyze the progression of visual field loss using sector analysis of the cumulative defect curve and other procedures.*
METHODS. *Visual fields of 260 glaucomatous eyes were analyzed over 2.8 years (SD = 1.2) with at least five examinations (mean 6.9; SD = 2.0) using Octopus 311 perimeter and TOP strategy. The authors applied Threshold Noiseless Trend (TNT) program, which performs local filtering of threshold to reduce fluctuation, and analyzed five criteria: 1) a score based on significant progression of eight sectors of the cumulative defect curve (CD); 2) a score based on the presence of points (PO) with significant progression; 3) global progression (GL) of all local deviations; 4) progression of mean defect (MD); 5) progression of the square root of loss variance (sLV). The authors estimated false diagnoses (FD), randomly reordering examinations of each patient. An index of focality of progression (FI) was obtained.*
RESULTS. *sLV presented low sensitivity and GL low specificity. CD and PO presented twice the sensitivity of MD, often proving earlier indicators. The authors observed significant progression of some of the three criteria in 17.5% of the cases when MD <6 dB and in 20.7% when MD >6 dB (FD=5.7%). Agreement between two criteria occurred in 6.8% of cases with MD <6 dB and in 11.6% when MD >6 dB (FD=1.9%). Result reproducibility in successive examinations was observed in 9.9% of cases (FD=1.3%). Focality of progression increased with MD.*
CONCLUSIONS. *PO and CD indicate suspected progression earlier than MD. Reproduction of results in successive examinations or agreement between criteria allows confirmation of progression. (Eur J Ophthalmol 2009; 19: 416-24)*

KEY WORDS. *Progression of visual field loss, Sector analysis, Cumulative defect curve*

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INTRODUCTION

Early detection of visual field progression in glaucoma is a clinical problem that has not yet been satisfactorily resolved. Most authors who have investigated this question highlight the absence of a generally accepted gold standard in this respect (1). The main limitation of studying visual field progression is its threshold fluctuation.
Regression analysis for quantifying progression was initially proposed by Holmin and Krakau (2). Mean defect (MD) is a reliable and sensitive procedure but produces results too late (1). A further limitation of this index is that it fails to differentiate between focal and diffuse evolution. Despite limitations, the study of progression of Octopus Loss Variance (LV) could provide information on focal and diffuse evolution when MD is below 15–17 dB. (It should be remembered that, in contrast to Octopus perimetry, Humphrey perimetry expresses pathologic deviation with

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a negative sign.) Above this range, the presence of absolute defects inverts the tendency to increased LV. This lack of linearity limits the use of this index, although some studies have reported better results with LV than with MD (3).

The results of works based on regression analysis may be improved using regression of mean sensitivity of certain zones of the visual field (4), point by point linear regression (5, 6), analysis of different sectors (1, 7), clustering of points with significant progression (8), separating MD of normal and pathologic zones (9), or observing result reproducibility in consecutive examinations (10). The presence of points with highly significant progression ($p<0.01$) has been considered a useful indicator in this respect (6, 10). It has been confirmed that the sum of the slopes of local deterioration, equivalent to the slope of MD, is useful for predicting evolution of visual field loss (11).

A great advantage of regression or "trend" analysis is its ability to detect improvements, frequently the result of the "learning effect" (12). Its major limitation is threshold fluctuation. This fluctuation may be reduced by mathematical procedures of spatial filtering (5, 13-15). Any possible loss of topographic information (16) is compensated by a substantial increase in stability of the results (17, 18). It is even more stable than that of combined expert opinion (19).

Only one study has included a global and simultaneous analysis of the progression of all threshold deviations over time (multivariate regression analysis) (1).

A second group of programs are based on the so-called "event analysis." A preliminary visual field range is established by two or three initial examinations of the patient, to define the normal variability of future results. Outstanding among these programs is the Glaucoma Change Probability Analysis designed for Humphrey Perimetry, which analyzes total deviations from normality or those represented in the Pattern Deviation Map. The program is reported to detect progression in the proximity of previous scotomas (20) and earlier than in regression-based models (6), but this has been widely questioned, even recently (21). Moreover, it is questionable whether the initial percentiles can be estimated exactly with so few examinations and, more importantly, this system is not capable of detecting improvements. Bayes' theorem has also been applied recently in a theoretical model to analyze progression (22).

Another group of procedures to measure progression is based on clinical trial criteria, attempting to detect increases in the number of points with defects over time, weighting those that appear in certain critical positions (essentially the arcuate area) or forming clusters (23). These are also event analyses and the various techniques are designed to pick up progression at differing stages of disease status. Examples are the Advanced Glaucoma Intervention Study (AGIS) (24), the Collaborative Initial Glaucoma Treatment Study algorithm (CIGTS), the Early Manifest Glaucoma Trial score (EMGT), and the Advanced Glaucoma Intervention Study algorithm. But they frequently produce mutually contradictory results and fail to detect improvement (25).

Mention should also be made of some attempts to use neuronal networks for the analysis of progression (26, 27).

The cumulative defect curve (CD) or Bebie curve (28) is a highly practical procedure for visually indicating the focal or diffuse characteristics of visual field defects. Its utility for measuring progression has not been sufficiently evaluated, but it seems that it may permit identification of focal progression before MD. Tendency oriented perimetry (TOP) (29) has been widely evaluated as a diagnostic strategy (30), and compared to other perimetric strategies (31). Although it produces a LV reduction which has been controversial (32, 33), it has not been evaluated for disease follow-up.

This study aimed to analyze five procedures of progression analysis using linear regression, previously applying a new process of spatial filtering to the visual fields performed with the TOP strategy (34). The filtering is based on the relations of interdependence of the points we analyze in glaucomatous visual field (35), reduces test-retest fluctuation, and makes the results of full threshold (bracketing) and TOP more similar. The criteria evaluated were 1) significant progression of eight sectors of the cumulative defect curve (CD); 2) the presence of points (PO) with significant progression of local deviations of threshold; 3) global progression (GL) of all local deviations (1) after filtering; 4) progression of mean defect (MD); 5) progression of the square root of loss variance (sLV).

METHODS

A total of 267 eyes of 145 patients with chronic open angle glaucoma, ocular hypertension, or suspected glaucoma were examined using the Octopus 123 perimeter (Interzeag AG, Schlieren-Zürich. Switzerland). Given the large simple size, both eyes were included (33). Sixty-one eyes presented ocular hypertension without perimetric or papillary defects, taking into account corneal thickness.

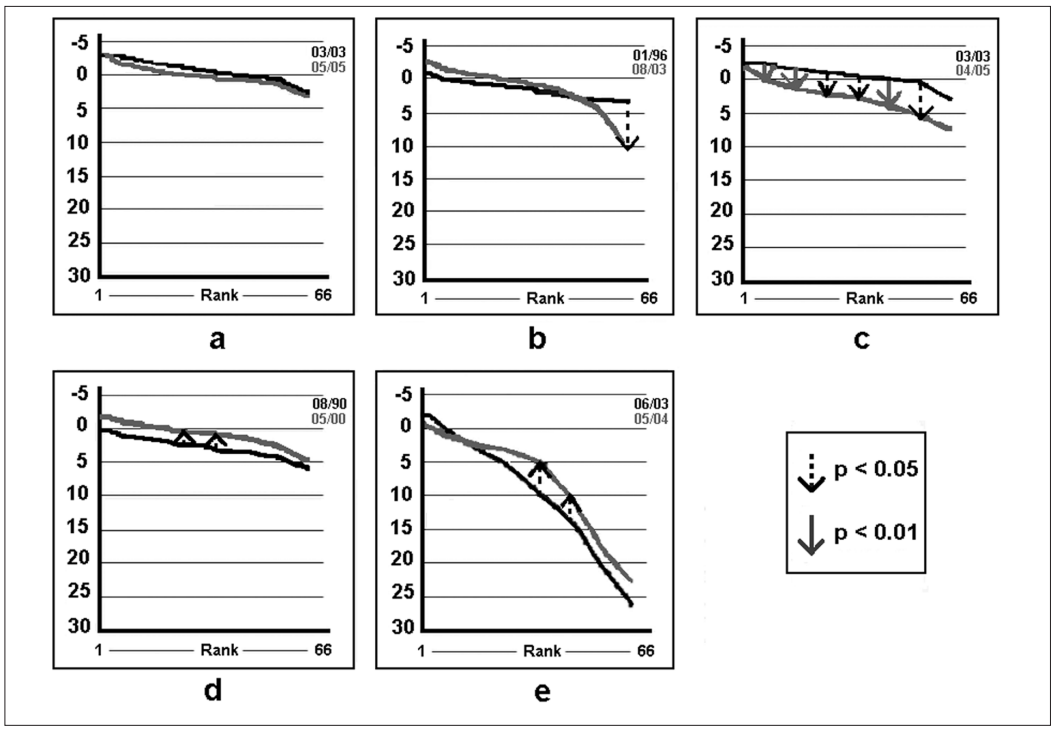

Fig. 1 - *CD curves representing local deviations in dB (y axis) from smaller to bigger, at the 66 examined points (x axis). The black line represents the initial CD curve while the grey line represents the final curve, calculated by sector regression. The CD curve allows the identification of* **(a)** *stability,* **(b)** *focal defects,* **(c)** *diffuse defects,* **(d)** *learning effect, or* **(e)** *mixed situations. The month and year of the first and last examinations are shown in the top right hand corner.*

The remaining patients presented specific signs of glaucoma, were receiving treatment, and were enrolled as they attended revision appointments; their previous examinations were recovered, without considering whether progression was suspected or not. Examinations were performed between July 1997 and November 2005.

The diagnosis of glaucoma was made by any of the following criteria: 1) glaucomatous appearance of the optic nerve (including a localized thinning or notch of the neuroretinal rim, cup-to-disc ratio >0.8, or vertical enlargement of the cup); 2) reproducible visual field defects on previous examinations on standard bracketing perimetry (MD >2 dB, LV >6 dB, or three or more contiguous abnormal points [p<0.05] in the arcuate area in the pattern deviation plot); 3) evidence of glaucomatous visual field progression; and/or 4) marked asymmetry between both eyes' visual fields or optic nerves (difference >0.2 of the cup-disc ratio, difference between eyes of >2 dB of MD value). Anterior chamber angle was open. Patients had no other ocular pathology.

Patients had previous perimetric experience with at least two examinations. Subjects using medication which could affect the visual field, with refractive errors higher than 6 diopters of spherical equivalent, or cataracts with visual acuity worse than 20/40 were excluded. The visual field tests were performed with distance refractive correction as required in the Octopus 123, and performed by the same two optometrists with wide experience in visual field examination.

The visual field indices analyzed included local deviations with respect to normal age-corrected threshold value, MD and sLV.

Analysis of progression was performed by our specifically designed program, called Threshold Noiseless Trend (TNT), which evaluates 66 points of the central visual field, equivalent to a program 32 without the upper and lower rows. For the analysis of CD, the 66 points of the curve were divided into eight sectors, each with eight points, except for the first and last ones, which had nine. Progression probability is shown by arrows (Fig. 1).

For the analysis GL progression, absolute scotomas were excluded from the study on appearance, and to calculate probability of change we applied Bonferroni correction.

sLV does not show linear behavior for the whole range of glaucoma. It increases linearly with MD up to 16–17 dB and decreases linearly for more severe defects. In order to use linear regression in the analysis of sLV progression, we rectified the relation between MD and sLV, to make it linear throughout its range by applying the

following empirical formula:

If MD >16.33, then sLV = sLV + ([MD–16.33]/0.84)

This formula produces acceptable linearity (Spearman r=0.89, p<0.001) and was obtained from 973 eyes (72 controls, 659 early and suspected open angle glaucomas, and 242 confirmed moderate and advanced glaucomas) collected for an independent study pending publication.

The program TNT gives information about the diffused or focal characteristic of the progression by means of a focality index (FI) which can have values between 0 and 10 dB. The FI is the standard deviation of the eight progression differences between the final and initial situations of the CD curve. If both curves (final and initial) are parallel, FI=0 dB. If there is maximum irregularity, FI is close to 10 dB.

To select cutoff points for each diagnostic criterion of progression (Tab. I), we estimated its tendency to produce false diagnoses (FD). For this, the examinations of each case were randomly disordered and the same type of analysis was applied, adjusting each criterion until FD was below 5%. In this way, the theoretical specificity of each criterion would be approximately 95%.

Statistical analyses not directly provided by the TNT program were performed using the MedCalc 7.3.0.1 program (MedCalc Software, Mariakerke, Belgium).

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from all participants and the study was approved by the Ethical Committee of our hospital.

TABLE I - THE FIVE CRITERIA OF PROGRESSION ANALYZED IN THIS STUDY

Criteria	
CD	Significant progression of cumulative defect curve sectors
PO	Local points with significant progression
GL	Global progression of all local deviations
MD	Progression of mean defect
sLV	Progression of the square root of loss variance

TABLE II - THE SUBJECTS INCLUDED IN THIS STUDY

Patients	Total = 145
Male	49
Female	96
Eyes	260
Right	125
Left	135
Mean MD <6 dB	109
Mean MD >6 dB	151
Initial age, yr	64.1 (SD = 14.3)
Initial MD, dB	9.5 (SD = 7.7)
Initial sLV, dB	4.2 (SD = 2.4)
Follow-up, yr	2.8 (SD = 1.2)
No. of examinations	6.9 (SD = 2.0)

RESULTS

Characteristics of the cases studied

Learning effect, defined as significant improvement in a sector of CD in the last examination of a series, was detected in 17 eyes (6.4%) of 15 patients. We excluded a mean 2.4 (SD = 1.8) initial examinations until this effect failed to occur. Seven glaucoma eyes had to be excluded from the study since there remained fewer than 5 examinations. Finally, we studied 260 eyes of 145 patients (Tab. II and Fig. 2).

Relation between MD and sLV

The correlation coefficient between MD and sLV in the 1,791 examinations performed was 0.67 (standard error = 1.72 dB). Correcting the value of sLV using the previously described empirical formula we obtained a correlation coefficient of 0.96 (standard error = 1.36 dB).

Cutoff selection

After randomly reordering the examinations, FD was below 5% in the progression of MD and sLV for p<0.05 in the linear regression of each index with respect to the date of the examination. Despite application of the Bonferroni correction, GL analysis produced an FD of 16.8%.

Using CD, the value of FD was below 5% applying the following criterion: positive progression = (V1x5)+V2–V3 > 1, where V1 is the number of sectors that worsened with p<0.01, V2 is the number of sectors that worsened with p<0.05, and V3 the number of sectors that improved.

Using PO, the value of FD was below 5% applying the following criterion: positive progression = (P1x5)+P2–P3 > 9,

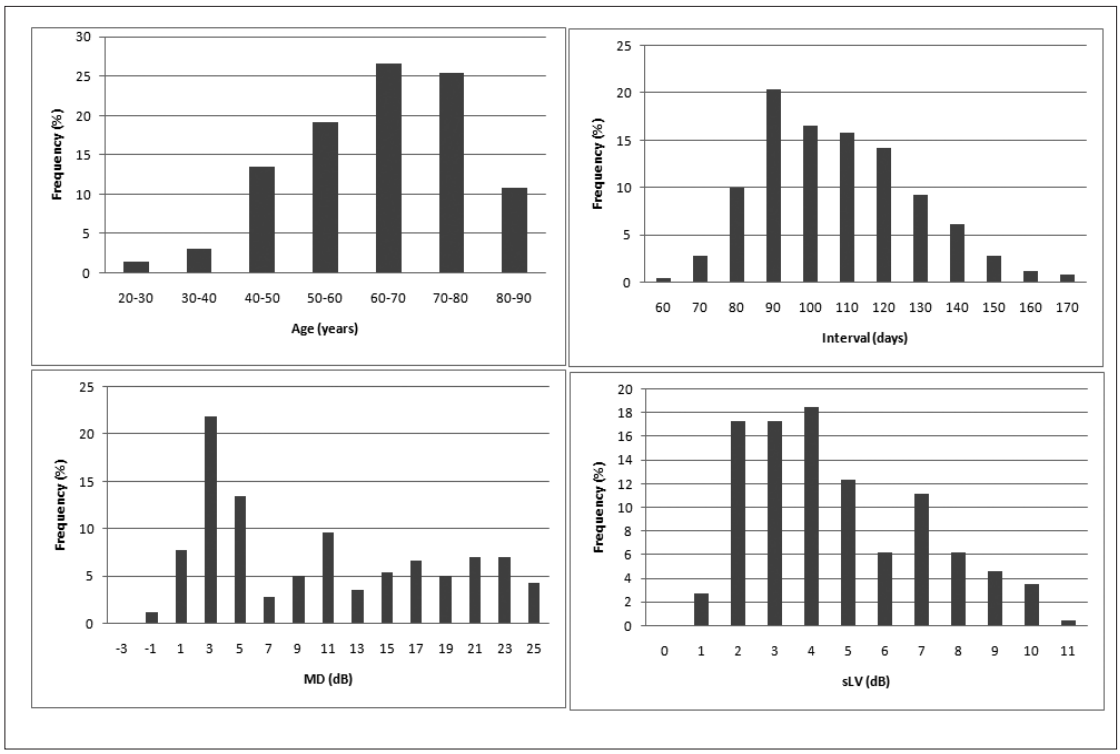

Fig. 2 - *Distribution of frequencies in the sample: age, interval between visits, and initial values of MD and sLV.*

where P1 is the number of points that worsened with p<0.01, P2 is the number of points that worsened with p<0.05, and P3 the number of points that improved.

Analysis of progression by indices

Figure 3 shows how the frequency of progression detection increased rapidly during the first 6–12 months of the mean follow-up (34 months), being very early and frequent for GL for p<0.05 and late and infrequent for MD and sLV. PO and CD began to detect progression after 12–18 months, with the number of cases detected increasing much more rapidly than with MD and sLV.

Diagnostic agreement between criteria

Given the low specificity of GL and the low sensitivity of sLV, they were excluded from the rest of the study.
Except in two cases, all diagnoses of progression performed with MD were also positive for PO or CD (Fig. 4). This occurred in 54.9% of cases simultaneously and in 45.1% of cases previously. We observed a moderate degree of agreement between CD and MD (kappa=0.58) and weak between CD and PO (kappa=0.40) and between MD and PO (kappa=0.31).

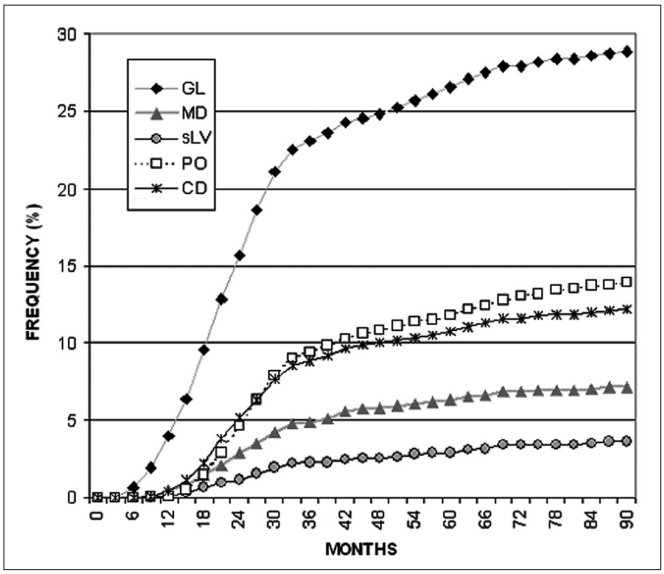

Fig. 3 - *Kaplan-Meier survival curves for detection of progression, for each of the five criteria evaluated.*

Figure 5 shows how the requirement of two criteria to indicate progression reduces by approximately half the number of cases with progression. Frequency also reduced by approximately half when agreement of three criteria was required.

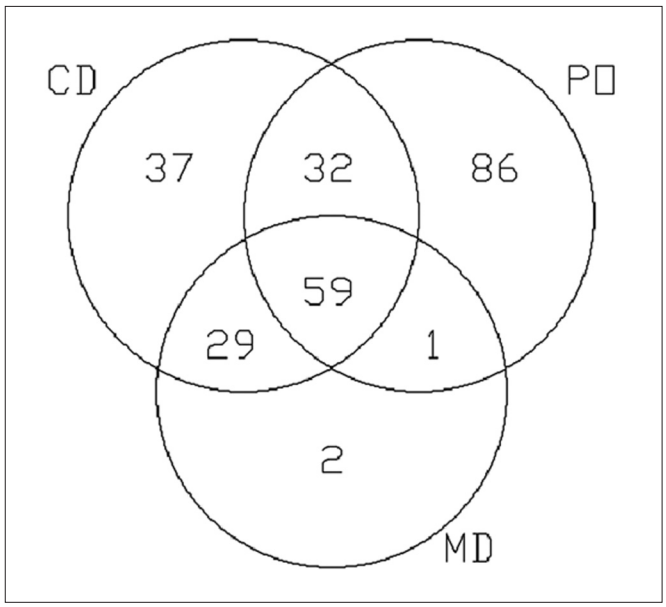

Fig. 4 - *Venn diagram indicating the amount of diagnostic agreement among CD, PO, and MD.*

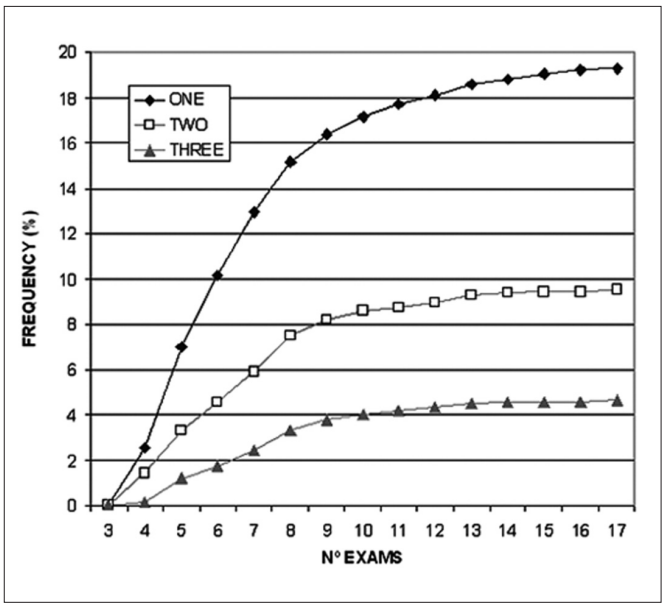

Fig. 5 - *Frequency of diagnoses of progression according to the number of criteria (CD, PO, and MD) and the number of examinations performed.*

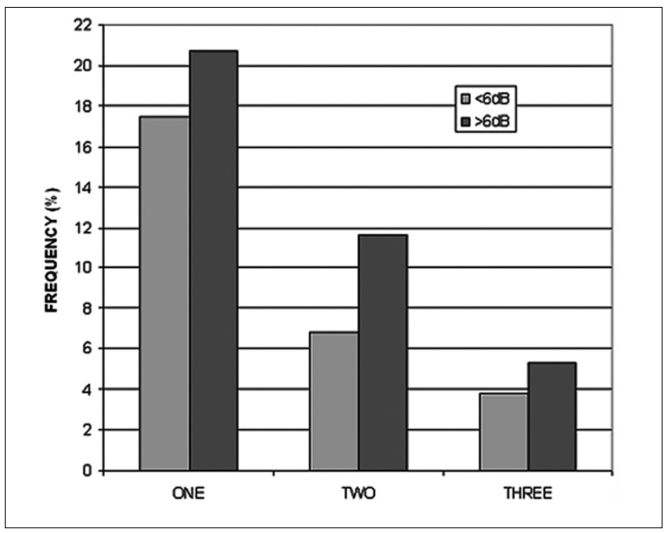

Fig. 6 - *Percentage frequency of diagnoses, for one or more coincident criteria of progression. Results of patients with mean MD below and above 6 dB are shown.*

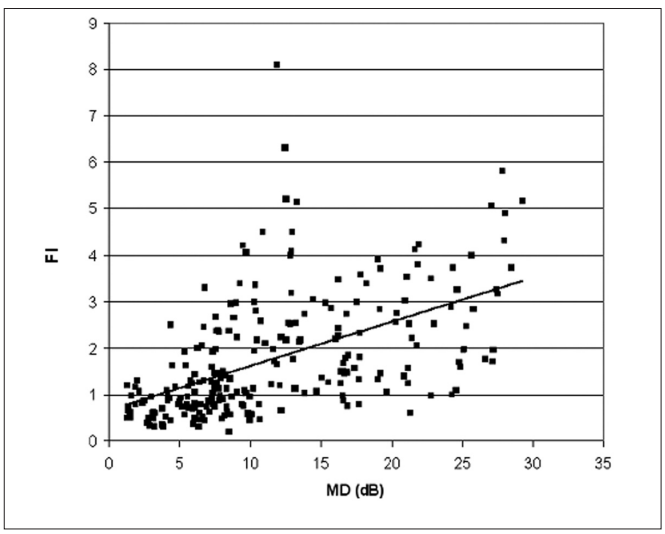

Fig. 7 - *Relation between MD and FI.*

After random reordering of examinations, the presence of one of the three criteria with significant progression was observed in 5.7% of the cases (theoretical specificity of 94.3%), agreement of two criteria in 1.9% (theoretical specificity of 98.1%), and of three criteria in 1.1% of the cases (theoretical specificity of 98.9%).

In patients with a mean MD <6 dB, the presence of one of the three criteria with significant progression was observed in 17.5% of the cases, and in 20.7% of those with mean MD >6 dB. Agreement between two criteria was also higher in patients with more advanced defects: 6.8% for MD <6 dB and 11.6% for MD >6 dB (Fig. 6).

Positivity of a single progression criterion was not reproduced in all successive examinations. This reproducibility

occurred in 9.9% of the cases, against 1.3% when the examinations were randomly reordered. Reproducibility increased with the number of examinations.

Defect slope

Mean defect slope for any positive criterion was 1.6 dB/year (SD=1.6), for two coinciding positive criteria 2.3 dB/year (SD=1.8), and for three positive criteria 2.7 dB/year (SD=1.7). When there are two or three coinciding criteria, the slope is significantly bigger than when there is just one ($p<0.01$).

We found no correlation between mean sLV in the first two examinations and mean defect slope in the first five ($r=0.03$, $p>0.05$).

Focality of progression

The value of FI increased significantly with the value of MD ($r=0.54$, $p<0.0001$) although we observed diffuse progression in patients with advanced glaucoma (Fig. 7).

DISCUSSION

The analysis of CD has proved useful to detect learning and allows eliminating some of the less reliable, initial examinations, as well as avoiding the masking of real progression.

Confirming the general opinion, the MD and sLV global indices produced a limited and late diagnosis in our study. If progression affects limited sectors of the visual field, its effect on MD is reduced by the influence of a large number of points that do not show progression. Despite verifying the efficacy of the procedure used to rectify the lack of sLV linearity throughout all the phases of glaucoma, this index proved of little use to detect progression in our study, in contrast to what was indicated in another article (3).

GL analysis proved to have very poor specificity. Randomly reordering the results of visual field tests, this system indicates false progressions, even when applying stricter p values than 0.05, which confirms the supposition that this system overestimates the value of p (1). The reason may be that thresholds of the glaucomatous visual field are not independent of each other (32) and linear regression procedure presupposes independence between the cases analyzed.

Sector analysis of the CD curve presents a high level of agreement with MD, and provides results earlier. Since thresholds and local deviations have random fluctuation, on ordering them from higher to lower, those situated at the same level in the same position of the curve in different examinations acquire much higher stability than the fluctuation measured at each position of the visual field. Local filtering prior to threshold reordering increases this stability even more. Consequently, fluctuation of points on the CD curve is much lower than the original thresholds, which greatly increases its potential to detect change. In addition, sector analysis of the CD curve allows a certain degree of averaging, which improves stability and at the same time distinguishes those areas with progression from those without, thus providing important information on the focal or diffuse nature of the progression.

PO presents sensitivity equivalent to that of CD, but with greater independence of MD, apparently detecting some cases with less increase of global defect, where the points that progress fail to affect the whole sector of the cumulative defect curve.

Considering these results, it seems reasonable to propose the presence of a positive criterion as suspected progression and its association with other criteria or its reproducibility over time as confirmation. In general this diagnostic system seems highly specific, requiring at least five examinations to rule out false detection of progression produced by chance (22).

Each of the diagnostic criteria presented a continuously increased frequency over time when analyzed separately. The diagnosis of “suspected progression” and that of “confirmed progression” presented a greater tendency to stabilization. A larger number of cases, examined over longer periods, or with a greater number of examinations per case is needed to determine the degree of conversion from suspected progression to confirmation.

The relatively low frequency of progression in our sample of patients may be due to the relatively short period of follow-up, which we attempted to offset by increasing the frequency of examinations, as well as the fact that most of our patients were stabilized by treatment. However, the frequency of signs of progression increased in the more advanced cases, clearly reducing the risk of false positives.

In previous studies we observed that sLV is a most useful index for early diagnosis of glaucoma (31, 36, 37). Other authors have indicated that its equivalent in Humphrey perimetry, PSD, is a risk predictor of conversion from ocu-

lar hypertension to glaucoma (38-40). We have not been able to show any relation between sLV obtained in the first examinations and subsequent progression in the case. Both observations are compatible. sLV and PSD are good diagnostic indices, which distinguish early between glaucomatous patients and normal subjects with ocular hypertension. Glaucoma patients, obviously, may show progression and healthy subjects do not, but in patients these indices do not constitute good indicators of risk of progression.

Theoretically, pattern deviation analysis could distinguish the diffuse component of progression from the local. We preferred not to address this possibility given the doubts about whether the correction of total deviation strictly corresponds to the diffuse component of the visual field (41), and because it has been observed that its use produces underestimation of the number of cases that progress (21). Analysis of the CD curve allows us to estimate the role of both components although with some limitations: the increase of the FI value with MD values is a logical consequence of the tendency of glaucoma to produce increasingly more profound and irregular defects. The presence of low FI values, especially in subjects with high MD values, requires increased vigilance and regular assessment of the state of the lens.

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