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Long-term perimetric fluctuation in patients with different stages of glaucoma

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ABSTRACT

Purpose: To evaluate the long-term perimetric fluctuation (LF) in patients with different stages of glaucoma according to the Glaucoma Staging System 2 (GSS2).

Methods: This multicenter retrospective study included 161 eyes of 161 stable glaucoma patients undergoing 4 visual field tests (Humphrey SITA-Standard program over the central 24° or 30°) over a 2-year period. For each patient, the stage of the disease was classified according to GSS2. LF was then calculated as the mean of the standard deviations of point-to-point threshold sensitivities in the four repetitions. LF in GSS2 stages was compared using *t*-test.

Results: LF progressively increased from stage 0 to stage 4, and then decreased at stage 5. Stage 4 had a peak of 3.19 ± 0.94 dB, with statistically significant differences compared with all the other stages. The lowest LF (1.65 ± 0.60 dB) was found for normal subjects, whereas similar data were found for borderline patients and those at stages 1 and 5 (2.09 ± 0.58 , 2.13 ± 0.57 , and 2.22 ± 0.89 dB, respectively; $P > 0.13$). Visual fields with generalized defects had lower LF (1.90 ± 0.81) than those with mixed (2.84 ± 0.87 , $P = 0.0003$) and localized (2.63 ± 0.72 , $P = 0.004$) defects.

Conclusions: In this study we showed that the lower was the visual field defect the lower was LF, except at stage 5 of GSS2. As test-retest changes exceeding LF could represent a sign of progression, we suggest to clinicians using this classification system to calculate LF, in order to better differentiate true progression from variability.

INTRODUCTION

The analysis of changes in standard automated perimetry (SAP) over time is a key element to detect glaucoma progression. Four main approaches to evaluate perimetric progression are available: clinical judgment of a series of tests, classification systems, event analysis, and trend analysis. All these approaches are limited by the “noise” of variability, which is the result of changes in the nature of the visual system, the testing situation, the features of the perimetric program, and the condition of the patient.¹

In a regression model of any perimetric parameter over time, regression line represents the expected change, whereas long-term fluctuation (LF) is an area of uncertainty both below (apparent worsening) and above (apparent improvement) this line. In the clinical practice, improvement of results due to LF has limited relevance (this is clearly an artefact because glaucoma cannot improve by definition), whereas worsening of results due to fluctuation is extremely important because LF can mask progression or even mimic glaucomatous deterioration.¹

Several mathematical models have been proposed for measuring LF;¹⁻³ studies of normal subjects, suspect glaucoma, and glaucoma patients have also shown that LF is predictable on the basis of mean defect (MD).¹⁻⁶

Among the strategies used to evaluate the amount of visual field defect and its changes over time, the Glaucoma Staging System (GSS) is gaining popularity due to its simplicity of use. By plotting MD against the pattern standard deviation (PSD) or the corrected PSD (CPSD), GSS classifies visual field results into 6 stages (from 0 to 5) and three types of defects (localized, mixed, generalized).⁷ Recently, the system has been implemented (GSS2) by introducing a borderline stage between stages 0 and 1.⁸

Although GSS2 may be useful in evaluating glaucoma changes at follow-up,⁹ currently there are no studies measuring LF at different stages of GSS2, which is the aim of this multicenter study.

MATERIALS AND METHODS

This retrospective study involved seven University Eye Clinics: Genoa, Milan (San Paolo Hospital), Parma, Pisa, Roma (G.B. Bietti Foundation), Siena (Italy) and Zaragoza (Spain). It was in adherence to the tenets of the Declaration of Helsinki; patients were informed about the study and gave informed consent for data treatment.

Patient selection

This study included patients with ocular hypertension (OH) or primary open-angle glaucoma (POAG), pseudoexfoliative glaucoma (PEG) or pigmentary glaucoma (PG) who fulfilled inclusion and exclusion criteria. Each of the 7 centers recruited 25 cases. One eye per subject was randomly selected if both eyes met the inclusion criteria.

The inclusion criteria were: 18 years of age or older; patients with OH, POAG, PEG, PG; stability of the disease during the study period (see below for definition); visual fields performed using the Humphrey Field Analyzer (HFA) II 750 (Zeiss Humphrey Systems, Dublin, Ca, USA) 24-2 or 30-2 test with Standard Swedish Interactive Threshold Algorithm (SITA) strategy; presence of at least 4 reliable tests (<25% false-positive responses, <25% false-negative responses, and <25% fixation losses) over a 2-year period. The exclusion criteria were: normal tension glaucoma; secondary glaucomas; the development of cataract or any pathology affecting visual acuity and visual field at any time during the study period; any change in the program used to test the patient at follow-up; learning effect at visual field during the study period; neurological disorders; systemic and ophthalmic disorders affecting SAP results or reliability. Diagnosis was based on chart review of medical history, biomicroscopy, gonioscopy, Goldmann applanation tonometry, and indirect fundus ophthalmoscopy.

POAG eyes were defined as having intraocular pressure (IOP) higher than 21 mmHg prior medication, glaucomatous optic neuropathy (diffuse neuroretinal rim narrowing with concentric enlargement of the optic cup, localized notching, or both)¹⁰ and repeatable abnormal results at SAP. OH were defined as having an IOP > 21 mmHg prior medication, no ocular pathologies and normal optic nerve head appearance and visual field results.

Stability of the disease

To be included, patients had to have no changes in mean IOP, medical regimen, optic nerve head appearance at ophthalmoscopy and SAP for the duration of the study. IOP was arbitrarily considered stable if changes of less than 20% in mean value (obtained from office-hour curves, i.e. 4 measurements between 8 AM and 4 PM) occurred compared with the first visit.

A battery of visual fields was considered stable if the first and the last tests showed absence of: 1) the development of a new scotoma (defined as three or more contiguous points with $P < 5\%$, or two or more contiguous points with $P < 1\%$); 2) the expansion of an existing scotoma into previously normal regions (defined as three or more contiguous points with $P < 5\%$, or two or more contiguous points with $P < 1\%$); 3) the deepening of an existing scotoma (defined as a decrease in the probability value or a reduction in sensitivity of at least 5 dB in three or more contiguous points, or 10 dB or more in at least two contiguous points¹¹); and 4) a worsening probability value for any perimetric index. Any change occurring in the second and third test was considered as variability.¹ Being stability a key point for a correct study conduction, all SAP were reviewed by an independent evaluator (PF), and 5 cases were excluded for progression.

The stage of the disease was classified according to the GSS2 using the mean of MD and PSD of the four tests. For each patient, all four tests were plotted into GSS2, and cases with borderline stage (ie. two tests falling into different stages) were excluded, a fact which occurred in 9 cases (Figure 1).

Statistical analysis.

LF was calculated as the mean of the standard deviations of point-to-point threshold sensitivities in the four repetitions using the following formula:

$$LF = \frac{1}{r} \sum_{i=1}^r \sqrt{\frac{\sum_{j=1}^n (x_j - \bar{x})^2}{n-1}}$$

where i (ranging from 1 to r , which was 54 for 24-2 program and 76 for 30-2 program) identifies the locations of the test, and j (ranging from 1 to n) is the number of tests per patient.

LF was then plotted against MD and PSD for each patient, Regression analysis was performed and correlation was calculated for the whole dataset. Thereafter, mean LF, standard deviation, and confidence intervals were calculated for each stage.

The analysis was performed with SPSS (version 13.0; SPSS Science Inc., Chicago, IL, USA). The *t*-test was used for comparisons; $P \leq 0.05$ was considered significant. Models of linear and second-degree regression were also used to inspect data associations.

RESULTS

The study was conducted on 161 Caucasian patients, whose demographics and perimetric data are given in Tables 1 and 2. The populations in the 7 sites had similar characteristics (similar age, MD, PSD, LF; $P > 0.10$).

MD was similar in patients with generalized and mixed defects ($P = 0.65$) and lower in patients with localized defects ($P < 0.001$). PSD was similar in patients with mixed and localized defects ($P = 0.39$) and lower in patients with generalized ($P < 0.001$, Table 2).

LF was plotted against MD and PSD. As shown by regression analyses in Figures 1 and 2, the best fitting curves for these variables were quadratic. LF had a trough of about 1.5 dB at MD of about +2 dB, it progressively increased to 3 dB, reaching a plateau for MD of about -12/-15 dB, and it progressively decreased to 1.5 dB when MD worsened up to -30 dB ($y = -0.0065x^2 - 0.1719x + 1.9054$; $R^2 = 0.30$). Similar findings were shown for PSD: LF had a trough of 1.5 dB for null PSD; it increased to 3 dB for PSD of 10 dB, and it progressively decreased to about 2 dB ($y = -0.0159x^2 + 0.3214x + 1.3256$; $R^2 = 0.26$).

LF mean values and 95% intervals of confidence are given in Table 3, box plot diagrams are given in Figure 4. LF progressively increased from stage 0 to stage 4, and then decreased at stage 5. Stage 4 had a peak of 3.19 ± 0.94 dB, with statistically significant differences compared with all the other stages ($P < 0.05$). Visual fields with generalized defects had lower LF (1.90 ± 0.81) than those with mixed (2.84 ± 0.87 , $P = 0.0003$) and localized (2.63 ± 0.72 , $P = 0.004$) defects. Table 4 also reports the details of LF for stage and type of defects; at each stage, mixed defects had the highest LF values.

159

160 **DISCUSSION**

161 Many strategies have been developed over the last years with the aim of providing an early and
162 accurate diagnosis of functional progression of glaucoma, but this task still remains tricky in a
163 number of cases due to the inability to distinguish true change from fluctuation. This clinical
164 problem is very relevant, as shown in the rigorous settings of a multicenter randomized study such
165 as the Normal Tension Glaucoma Study, on which a false call of progression of more than 50%
166 was found.¹²

167 LF is inborn on a psychophysical test such as perimetry, and it is therefore impossible to
168 get over it even at optimal clinical conditions. Mathematical models to soften the effect of LF and to
169 stabilize a series of visual fields have been recently reported,¹³ but the best way to reduce
170 variability is to reduce the clinical sources of the problem. Efforts should focus on adopting ideal
171 testing conditions (calm and comfortable room, mild illumination, use of standard operating
172 procedures) and the same perimetric strategy over time (LF largely varies between perimetric
173 strategies¹⁴).

174 Our study aimed at calculating the amount of LF in glaucoma patients with different GSS2
175 stages, which is, to the best of our knowledge, an unexplored issue. In theory, clinicians using this
176 classification system would find our data helpful to discriminate early glaucoma progression to
177 fluctuation.¹

178 As expected, patients with normal fields had low LF values (CIs ranging from 1.40 to 1.90
179 dB), with small overlap with borderline cases (inferior CIs of 1.80 dB) and glaucoma cases at stage
180 1 (1.86 dB).

181 An interesting finding of our paper was that borderline patients had MD similar to normal
182 subjects (Stage 0), and LF comparable with stage 1 (Table 3), despite a difference of more than 2
183 dB in MD and of more than 0.5 dB in PSD (Table 2). In other words, high LF values might be used
184 to predict the presence of early disease in borderline cases with normal MD. This finding needs
185 verification by properly designed studies.

Our paper confirmed that the relation between MD and LF is curvilinear and not linear (Figure 2).^{2,15} LF progressively increased from stage 0 to stage 4, it reached a plateau for MD of about -13 dB, and then decreased when glaucoma defect became more diffuse (stage 5 had intervals of confidence similar to stage 1). This curve resembles the curvilinear relation between MD and PSD described by Pearson et al.,¹⁶ because they share at least two common determining factors.

The first factor is the asymmetry of the Bebie curve, which increases as long as the glaucoma defect becomes more localized, and progressively decreases in more advanced stages of the disease, when both hemifields are involved. PSD is a direct measure of the asymmetry of the hill of vision with respect to normal, age-matched fields. As locations on the edge of the defect have higher variability,¹⁷ when a localized defect enlarges, the edge of the scotoma becomes larger and LF increases, as shown by several studies.^{2,3,5,15,18-20}

When the defects involve both hemifields, the edge of the scotomas becomes even larger, and one would therefore expect LF to increase. Actually, based on our data, LF progressively decreases, probably because the effect of the enlargement of the absolute scotoma (which fluctuates less than a relative scotoma¹⁷) is prevalent as both hemifields progressively deteriorate.

The second factor is a limitation of perimetry for high MD values. At the “bottom of the scale”, very deep scotomas may be judged absolute by the perimeter; this is due to insufficient stimulus size and luminance to stimulate the damaged ganglion cells. As a consequence, the corresponding points can fluctuate only above their average sensitivity but not below it (inferior fluctuation is not tested being sensitivity null for the perimeter). Also for this reason, both LF and PSD get reduced for high MD values.

Caution is required when using our data in the clinical settings. Although our dataset was clinical-based (the study was a retrospective analysis of data collected in glaucoma patients undergoing routine visits and visual field tests every 6 months), a fixed number of tests was chosen. Different LF values would be found if a variable number of tests was considered. Also, we excluded patients with different GSS2 stages at the beginning and the end of the study, although changes of type and stage can occur even in stable patients. Subgroup analysis was of limited

relevance due to the small number of cases ($n < 5$) falling in stages 1L, 2G, 3G, 4G, 5L. Our study is not informative on patients with normal tension glaucoma or secondary glaucoma, although GSS2 is useful also to monitor these patients.

A strength of the study was the multicenter design; tests were double-checked to exclude progression and similar inter-site demographics, perimetric and variability data were found. As opposite to other studies on perimetric fluctuation which used computer-simulated dataset or visual fields obtained over a short period of time, in our study routine intervals of time of 6 months were maintained between tests repetitions.

In summary, LF is a key-point to ascertain perimetric stability or progression, regardless of the strategy used to analyze visual field tests. This parameter can be easily calculated for each patient and it may provide useful information in a number of cases. We suggest to clinicians using GSS2 to calculate LF at least in patients with suspect progression, in order to obtain an earlier and more accurate diagnosis.

230 **Table 1. Demographics of study participants.**

231

232 **Ocular hypertension Glaucoma**

233

234 Number of patients (%) 41(25%) 120 (75%)

235 Female/Male, n 9/12 66/54

236 Age, mean±SD (years) 53±12 64±10

237 Range (years) 34-70 46-85

238 Diagnosis (n=161)

239 Ocular hypertension (n, %) 41 (25%)

240 Primary open-angle glaucoma (n, %) 100 (87%)

241 Pseudoexfoliative glaucoma (n, %) 15 (8%)

242 Pigmentary glaucoma (n, %) 6 (5%)

243

244 **Table 2. Perimetric data of study participants based on GSS2 staging.**

245

Stage	n (%)	MD, dB (mean ± sd)	PSD, dB (mean ± sd)
0	21 (13%)	+0.51 ± 0.95	1.57 ± 0.51
borderline	17 (11%)	-0.13 ± 1.23	2.28 ± 0.73
1	17 (11%)	-2.31 ± 1.30	2.75 ± 0.94
2	18 (11%)	-4.53 ± 1.41	4.80 ± 1.59
3	31 (19%)	-7.70 ± 1.94	8.39 ± 1.90
4	32 (19%)	-12.94 ± 2.68	11.83 ± 2.56
5	25 (16%)	-22.39 ± 4.18	9.75 ± 3.78
Generalized	17 (11%)	-12.66 ± 11.96	3.41 ± 2.30
Mixed	72 (45%)	-12.35 ± 6.41	8.79 ± 3.43
Localized	34 (21%)	-6.74 ± 4.08	9.55 ± 3.94

246

247

Table 3. Long-term perimetric fluctuation and intervals of confidence.

Stage	LF, dB (mean $\pm$ sd)	95%-IC, dB
0	1.65 $\pm$ 0.60	1.40 – 1.90
borderline	2.09 $\pm$ 0.58	1.80 – 2.38
1	2.13 $\pm$ 0.57	1.86 – 2.40
2	2.52 $\pm$ 0.72	2.19 – 2.85
3	2.80 $\pm$ 0.68	2.56 – 3.04
4	3.19 $\pm$ 0.94	2.87 – 3.52
5	2.22 $\pm$ 0.89	1.87 – 2.57
Generalized	1.90 $\pm$ 0.81	1.51 – 2.28
Mixed	2.84 $\pm$ 0.87	2.63 – 3.04
Localized	2.63 $\pm$ 0.72	2.39 – 2.88

Inter-group t-test, P-values

Vs	0	Borderline	1	2	3	4
5	0.05	0.13	0.68	0.23	0.01	0.0002
4	<0.0001	<0.0001	<0.0001	0.007	0.05	
3	<0.0001	<0.0001	0.0007	0.19		
2	<0.0001	0.003	0.08			
1	0.15	0.62				
borderline	0.18					

Generalized v Mixed, **P=0.0003**

Generalized v Localized, **P= 0.004**

Mixed v Localized, P=0.21

258 **Table 4. Test-retest perimetric variability for stage and type of defects.**

259

Stage	n	LF, dB (mean $\pm$ sd)
1 localised	4	1.68 $\pm$ 0.58
mixed	5	2.43 $\pm$ 0.60
generalised	8	2.16 $\pm$ 0.44
2 localised	7	2.55 $\pm$ 0.71
mixed	9	2.58 $\pm$ 0.73
generalised	2	2.15 $\pm$ 1.03
3 localised	12	2.70 $\pm$ 0.47
mixed	18	2.88 $\pm$ 0.81
generalised	1	2.49
4 localised	10	3.07 $\pm$ 0.69
mixed	22	3.25 $\pm$ 1.05
generalised	0	n/a
5 localised	1	1.81
mixed	18	2.53 $\pm$ 0.66
generalised	6	1.37 $\pm$ 1.03

260

LEGENDS TO FIGURES

Figure 1. Study flow. Gray box, patients excluded from the study.

Figure 2. Regression analysis of mean defect vs long-term fluctuation.

Figure 3. Regression analysis of pattern standard deviation vs long-term fluctuation.

Figure 4. Box plot diagrams of long-term fluctuation for different GSS2 stages. G, generalized defects; M, mixed defects; L, localized defects; circles, outliers.

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FIGURE

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