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Evaluation of Visual Field and Perg Parameters of Glaucomatous Patients Under Oral Supplement By Forskolin, Magnesium, Homotaurin, L-Carnosin, Vitamins B1, B2, B6 And Folic Acid

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Abstract: ***Forskolin, magnesium, homotaurin, L-carnosin, vitamins B1, B2, B6 and folic acid are the main ingredients of a food supplement commercially available. This drug contributes to a small reduction of IOP in glaucomatous patients who are poorly responsive to multitherapy treatment. The aim of this study is to evaluate a possible change of visual field and pattern-electroretinogram (PERG) parameters after oral supplement of this drug.***
PATIENTS AND METHODS: This is a single center, retrospective study. It was conducted on files of 20 (10 M, 10 F) treated glaucomatous patients and 20 (10 M, 10 F) untreated controls. All these patients were affected by open-angle glaucoma under monotherapy but this association was supplemented twice a day to 20 patients as long as 12 months. The ophthalmological data (IOP, pachymetry, visual field assessment by FDT 30-2 strategy pattern standard deviation, PERG) were checked at time 0, 3 6, 9 and 12 months from the beginning of the oral therapy. The statistical analysis was performed by descriptive statistics, one-way ANOVA and Wilcoxon test. Results were considered significantly different when p<0.05.
RESULTS: The two groups were age and sex-matched (p=0.335). The two groups were also matched as for pachymetry (p=0.187). The visual field parameter (mean deviation and pattern standard deviation by FDT 30-2 strategy) was statistically significantly different only at time 12 months (p=0.04). The PERG amplitude increases by 16.12%±2.6 at time 9 months and fovea sensitivity by 16.57%±3.2 at time 6 months (p<0.05).
CONCLUSIONS: Our preliminary data stress the neuroprotective effect of the association of forskolin, magnesium, homotaurin, L-carnosin, vitamins B1, B2, B6 and folic acid from a campimetric and electrophysiological point of view.
.FINANCIAL DISCLOSURE: The Author has no financial disclosure in any drug used in this paper.

Keywords: Forskolin, neuroprotection, PERG, visual field.

1. Introduction

Forskolin (a natural compound present in the extract of the plant Coleus Forskohlii), magnesium, homotaurin, L-carnosin, vitamins B1, B2, B6 and folic acid are the main ingredients of a food supplement commercially available. This drug shows to reach the ocular district through the oral route, where they can act in synergy with topical pharmacological treatment, and contribute to the control of intraocular pressure (IOP) [1]. It was also designed and evaluated as a thermoreversible in situ gelling system for ophthalmic drug delivery [2]. They can also contribute to a better control and a further small reduction of IOP in patients who are poorly responsive to multitherapy treatment [3]. From a biological point of view, increased intracellular cAMP mediated by forskolin led to a significant increase in extracellular adenosine production. This pathway might play an important role in the homeostatic regulation of outflow resistance in the porcine trabecular meshwork (PTM) and in human non pigmented ciliary epithelial cells. These experimental data suggest a novel mechanism by which pathologic alteration of TM, such as tissue rigidity, could lead to abnormal elevation of IOP in glaucoma [4]. Forskolin is a receptor-independent adenylate-cyclase activator. It has been described that elevation of cAMP inhibits the activation of the Rho protein. Forskolin-mediated activation of cAMP contributes to neuronal cell survival and growth [5].

Homotaurine is a derivative of taurine. It acts as GABA-A neurotransmitter. It inhibits NMDA receptor upregulation and it counteracts MAPK activation and it inhibits Aβ-amyloid deposits in Alzheimer disease. Carnosin is an antioxidant able to scaveng free radicals and binds heavy metal, such as iron, zinc and copper. Indeed, it protects from glutammate excitotoxicity. It binds soluble Aβ-amyloid in Alzheimer disease as homotaurine. At last but not least, this association appears to be protective for the ocular surface, contributing to restore a normal equilibrium of the tear film in glaucomatous patients in which toxic agents such as BAK had determined alterations of its homeostasis [6]. Instead, in mild to moderate Alzheimer disease tramiprosate showed only a trend towards slowing the decline of this neurodegenerative disease [7]. In Neurology and in Ophthalmology also nicergoline and citicoline can be used as neuroprotective drugs [8],[9].

Aim of this paper is to prove a direct neuroprotective effect of this pharmacological association.

2. Patients And Methods

The design of this study is single center, retrospective. It was performed in the Catholic University of Roma from 01-01-2013 till 12-31-2013. The study was conducted in full accordance with the tenets of the Declaration of Helsinki. As it is a single center study, it was not mandatory the registration on clinicaltrial.gov website.

3. Patients

Files from twenty adult glaucomatous patients (Group A) (10 M, 10 F) (average age: 61.3 years ± 19.88 years) (pachymetry: 536.6 μm ± 29.2 μm) [Table I] who received an oral supplement of this association twice a day up to 12 months from the baseline were checked in this clinical trial.
Files of twenty adult glaucomatous patients (Group B) (10 M, 10 F) (average age: 70.5 years ± 6.803 years) (pachymetry: 553.1 μm ± 45.01 μm) [Table I] who did not receive
any oral supplement were checked.
Patients were included if they had: older than 18 years, early open-angle glaucoma in monotherapy with glaucoma hemifield test (GHT) borderline a/or out of normal limits on Humphrey Matrix FDT performed at least twice in a month (Table II). Their IOP was always below 18 mmHg during diurnal tonometric curve.
Patients were excluded if they had: presence of cardiovascular diseases, diabetes mellitus; presence of advanced perimetric defect according to Brusini's FDT Staging System [10]; filtration surgery or other ocular surgeries in the previous six months.

4. Methods

The ophthalmological assessment, including visual acuity assessment, slit-lamp biomicroscopy, Haag-Streit applanation tonometry, Orbscan pachymetry, mean deviation (MD) and pattern standard deviation (PSD) by FDT 30-2 strategy assessment, PERG according to the ISCEV standard and fundus oculi was checked at basal time and at time 3, 6, 9 and 12 months. Transient PERG was performed (3Hz). The amplitude assessment was performed between P50 and N95. For PERG recording, DTL electrodes were put in the inferior fornix. Reference electrodes were placed in the ipsilateral external canthus. The ground electrode was placed on the forehead. The skin was prepared with a soft brushing and a conductive ointment. Black and white checkerboard was used with a stimulus of 40 minarc in a field of 16°. Contrast sensitivity was over 80%. The luminance of the white areas were over 80 cd/sm. The global screen luminance did not vary during the frames inversion (isoluminance). The room luminance was low. The pupils were myotic and there was a target in the middle of the screen. The patients received an appropriate visual acuity correction. To get a stable wave, the test was performed after 150 stimuli. All the patients received a questionnaire about their prospective and retrospective memory [11].

5. Statistical analysis

The descriptive statistics was performed to compare the distribution of values in both groups as for age and pachymetry. One way ANOVA was used to compare the statistical data about age and pachymetry in both groups. The Wilcoxon test was performed to compare the mean deviation and pattern standard deviation of FDT 30-2 visual field assessments at time 12 months in both groups. The Wilcoxon test was also performed to compare the PERG amplitude and fovea sensitivity at basal time and after 3, 6, 9 and 12 months. Results were considered significantly different when $p<0.05$.

6. Results

All the patients were under good tonometric control on monotherapy. Their IOP was always below 18 mmHg at every check. The two groups (A and B) were age and sex-matched ($p=0.335$). They were also pachymetry-matched ($p=0.187$). At the end of the clinical trial their FDT pattern standard deviation was significantly statistically different ($p< 0.04$) in Group A patients, supplemented by forskolin, magnesium, homotaurin, L-carnosin, vitamins B1, B2, B6 and folic acid twice a day as long as 12 months (Table III) (Figg. 1-4). The PERG amplitude increased by 16.12 %±2.3 at time 9 months and the fovea sensitivity increased by 16.57 %±3.2 at time 6 months (Table IV) ($p<0.05$). The memory questionnaire showed an improvement of 4.4 points (S. D. 1.647, range: 2-7) during the same period of therapy in Group A vs Group B ($p=0.04$).

7. Discussion And Conclusions

This pilot study clearly indicated that this oral supplement may have a neuroprotective effect on the main parameters of the visual field in patients affected by early-stage glaucoma after 12 months of therapy. The PERG amplitude increased by the month 9 and the fovea sensitivity by month 6 from baseline in a statistically significant way ($p<0.05$). From the psychological point of view, there is a small increase of points in the memory questionnaire as for the control group. Apart from the improvement of the iatrogenic ocular surface disease, this association may also contribute to increase patients compliance during their pharmacologic treatment. The strength of this study is that it is the first in the international Literature to prove a neuroprotective effect of this pharmacological association from a campimetric and PERG point of view. Its limitations are: the small number of patients enrolled andonly one year follow-up. This is the reason why the Author considers it as a preliminary report.

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Tables And Figures

N	MEAN AGE	PACHIMETRY
GROUP A (10 M; 10 F)	**61.3 ±19.88y.**	**536.6±29.2 µm**
GROUP B (10M; 10F)	**70.5±6.803 y.**	**553.1±45.01 µm**

TABLE I: Demographics and pachymetry. Group A: treated glaucomatous patients. Group B: untreated glaucomatous patients.

DRUG	GROUP A	GROUP B
BIMATOPROST	**6**	**8**
LATANOPROST	**6**	**6**
TAFLUPROST	**6**	**4**
TRAVOPROST	**2**	**2**

***TABLE II: Therapy*.** Group A: treated glaucomatous patients. Group B: untreated glaucomatous patients.

RESULTS

N	PRE MD	POST MD	p	PRE PSD	POST PSD	p
20 (Group A)	**+1.2**	**+1.3**	**N.S.**	**+2.65**	**+3.29**	**<0.04**
20(Group B)	**+1.1**	**+1.2**	**N.S.**	**+2.50**	**+2.45**	**N.S.**

TABLE III: Results after 12 months from baseline of FDT 30-2 strategy assessment. Group A: treated glaucomatous patients. Group B: untreated glaucomatous patients.

Untreated PERG amplitude	100%+/-7,2	100,14+/-2,3	94,90+/-1,8	95±10
p vs T0		NS	NS	NS
Treated PERG amplitude	100%+/-3,2	100,8%+/-3,1	112.12%±2.5	116.11
p vs T0		NS	NS	NS
p untreated/ treated	NS	NS	NS	NS
Time	T0	T1(3months)	T2(6 m)	T3(9 m)
Untreated Fovea sensitivity	100%+/-7,9	106,82%+/-7,9	97,92%+/-9,9	95.1%±9.8
p vs T0		NS	NS	NS
Treated Fovea sensitivity	100%+/-9,4	107,37+/-9,1	116,57+/-3,2	114.1%±9.8
p vs T0		<0,05	<0,05	<0.05
Time	T0	T1(3 m)	T2(6 m)	T3 (9 m)
P untreated/ treated	NS	NS	NS	NS

TABLE IV: Electrophysiological results. Group A: treated glaucomatous patients. Group B: untreated glaucomatous patients.

Legenda:

M.D.: Mean deviation; N: number of patients; NS: not significant; PSD: pattern standard deviation; S.D.: standard deviation; y.: years.

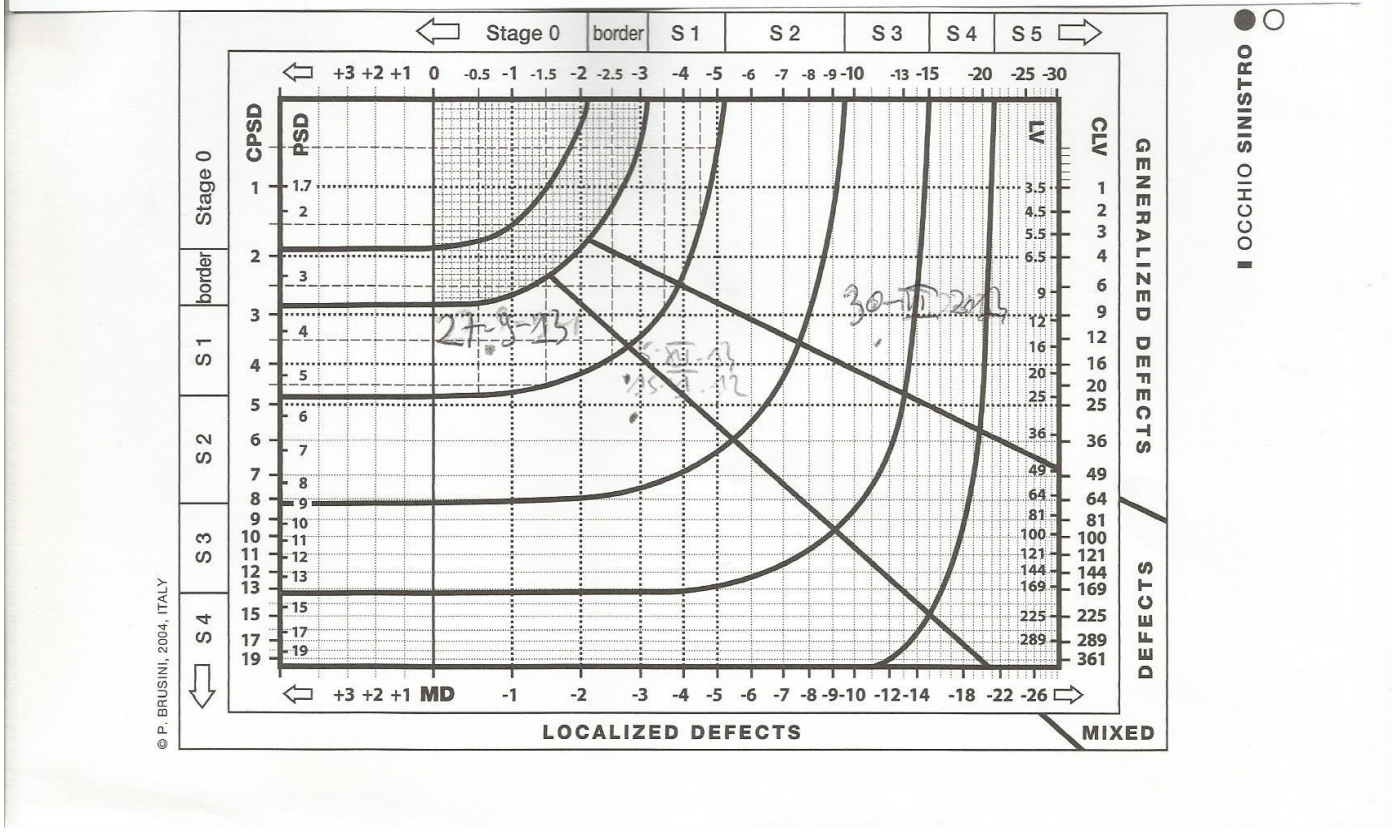
FIGURES

Fig. 1Right eye (RE) follow-up of patient # 3 S.G., male, 42 years old under oral supplement by forskolin, magnesium, homotaurin, carnosin,vitamins B1, B2, B6 and folic acid according to Brusini Glaucoma Staging System after 12 months.

Fig.2. Left eye (LE) follow-up of patient # 3 S.G., male, 42 years old under oral supplement by forskolin, magnesium, homotaurin, L-carnosin, vitamins B1, B2, B6 and folic acid according to Brusini Glaucoma Staging System after 12 months.

Fig.3.Right eye (RE) follow-up of patient # 6 R.S., female, 67 years old under oral supplement by forskolin, magnesium, homotaurin, L-carnosin,vitamins B1, B2, B6 and folic acid according to Brusini Glaucoma Staging System after 12 months.

Fig.4.Left eye (LE) follow-up of patient # 6 R. S., female, 67 years old under oral supplement by forskolin, magnesium, homotaurin, L-carnosin, vitamins B1, B2, B6 and folic acid according to Brusini Glaucoma Staging System after 12 months.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S 2
S 3
S 4
S 5
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CPSD
PSD
LV
CLV
1 1.7 2 3 4 5 6 7 8 9 10 11 12 13 15 17 19
3.5 4.5 5.5 6.5 9 12 16 20 25 36 49 64 81 100 121 144 169 225 289
1 2 3 4 6 9 12 16 20 25 36 49 64 81 100 121 144 169 225 289 361
GENERALIZED DEFECTS
SLOPED DEFECTS
Stage 0
border
S 1
S 2
S 3
S 4
+3 +2 +1 MD -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -12 -14 -18 -22 -26
LOCALIZED DEFECTS
MIXED
OCCHIO SINISTRO
© P. BRUSINI, 2004, ITALY

Fig.1

Glaucoma Staging System 2

DATA 23-10-2013

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TIMOLOL 2% BL

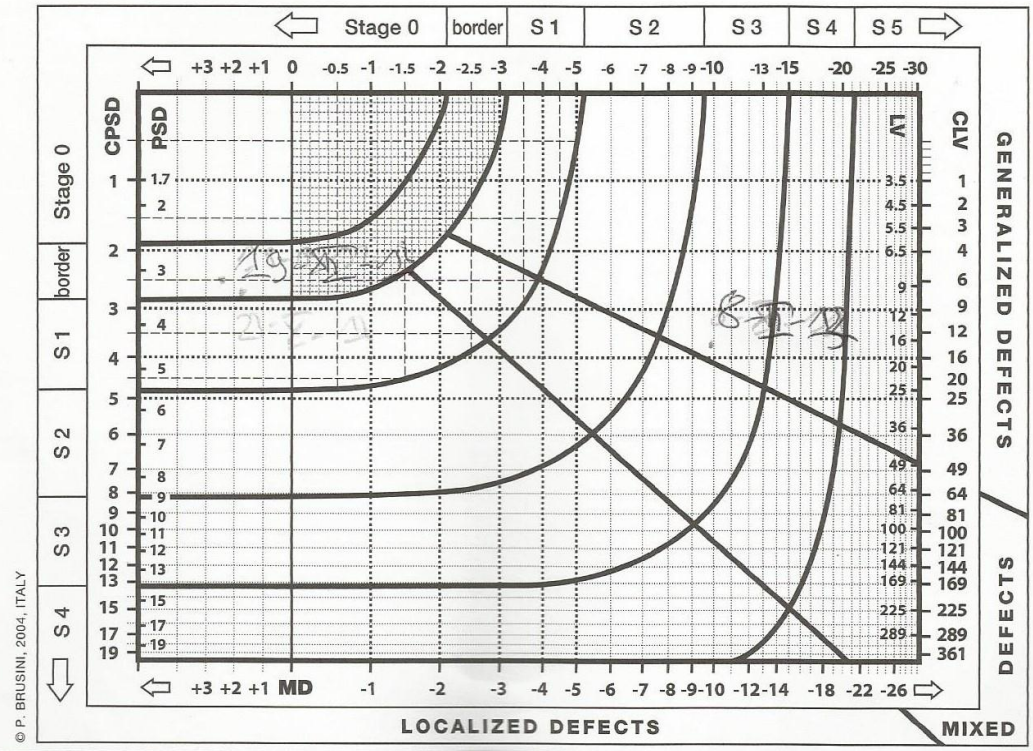
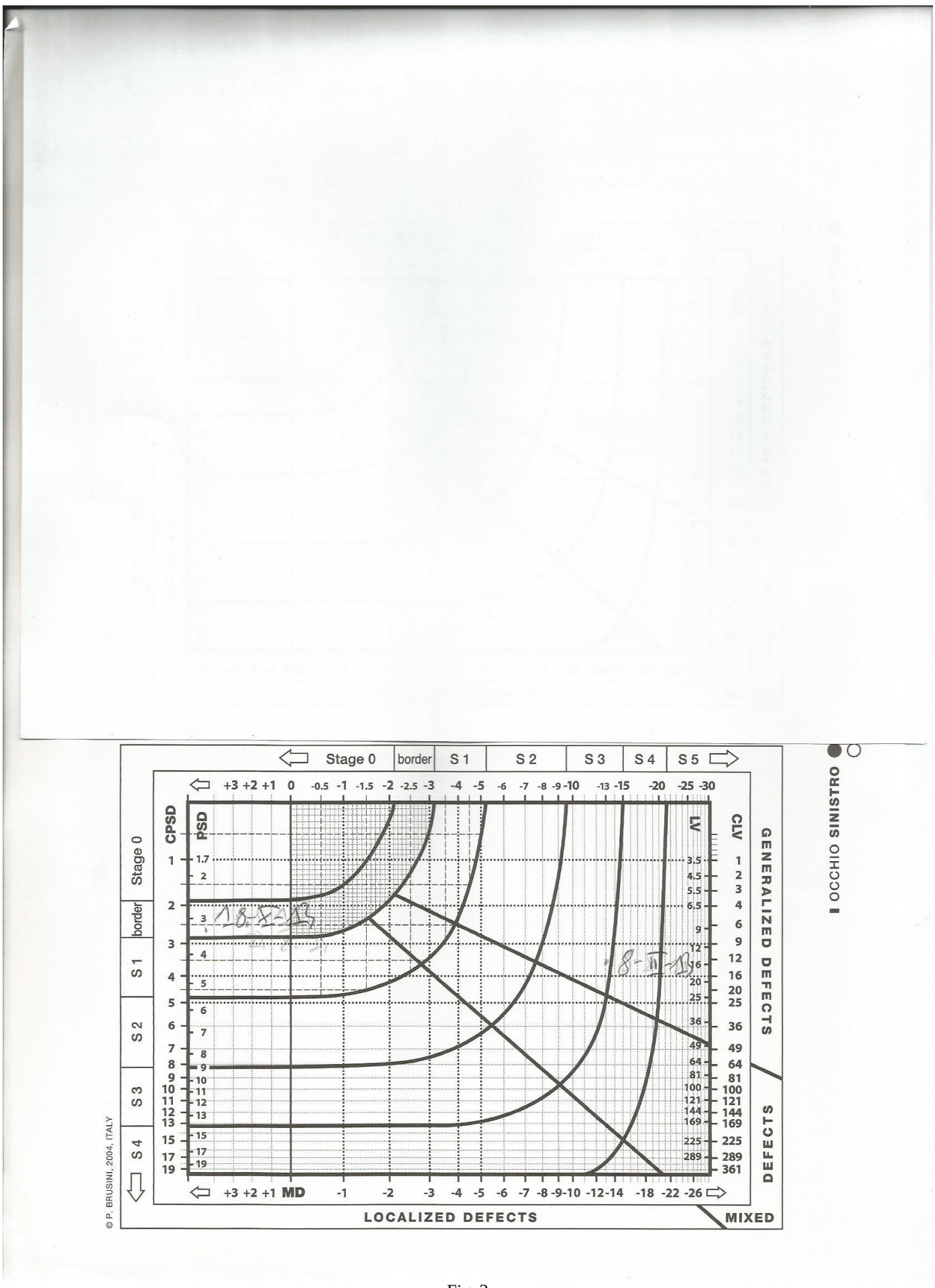


Fig.2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S 2
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CPSD
PSD
LV
CLV
GENERALIZED DEFECTS
SLOPED DEFECTS
+3 +2 +1 MD -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -12 -14 -18 -22 -26
LOCALIZED DEFECTS
MIXED
OCCHIO SINISTRO
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Fig. 3

Glaucoma Staging System 2

DATA 27-3-2014

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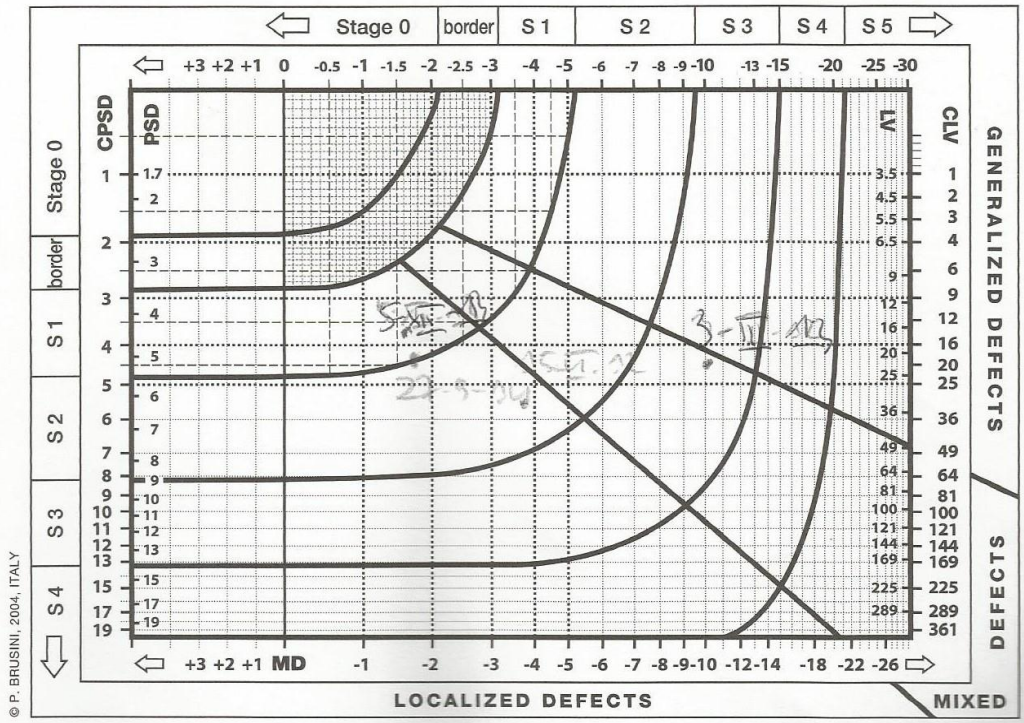
DIAGNOSI [illegible]



OCCHIO DESTRO

Fig. 4