Romanian Journal of Ophthalmology, Volume 60, Issue 3, July-September 2016. pp:174-180

GENERAL ARTICLE

Risk factors and long term progression in open angle glaucoma patients

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Accepted: July 19, 2016

Abstract

Aim: Investigation of perimetric progression rate and associated risk factors in open angle glaucoma, in clinical practice.

Methods: Retrospective study based on clinical charts reviews of patients with primary open angle glaucoma (POAG) being followed for > 5 years with >/ = 5 SITA Standard visual fields. Demographics, visual acuity (VA), central corneal thickness (CCT), intraocular pressure (IOP) and IOP variation, treatment (number of medications), visual fields and associated systemic pathologies were recorded. Patients were followed at every 3-6 months, when identical tests were performed. VF progression rate was calculated as slope of mean deviation (MD) over time by Glaucoma Progression Analysis software.

Results: 121 eyes of 121 patients with POAG were included in the study and were followed for a mean period of 68.81 months (SD +/ - 31.7). The mean MD at start was -3.55 dB (SD +/ -5.19)., with a mean number of VF tests of 9.3+/ -2.9. Progression rate reached -0.21 +/ -0.1 db/ year. Mean IOP of all visits decreased over time from 18.20 mmHg to 16.53 mmHg ($p<0.05$). Systemic factors like positive history of hypertension reached statistical relevance in terms of increased risk for glaucoma progression, but only after age and sex were corrected. MD slope was explained in ANOVA univariate analysis, by the level of MD at baseline, IOP baseline, number of topical medications and CCT in a proportion equal to 71.7% ($p=0.004$).

Conclusion: Rate of visual field changes in POAG was correlated and dependent on the baseline MD level, IOP at baseline, number of topical medications and a thin CCT.

Keywords: glaucoma progression, risk factors, Glaucoma Progression Analysis

Introduction

Glaucoma represents an optic neuropathy that can lead to optic nerve irreversible damage and blindness. Among all glaucoma types, primary open angle glaucoma is the most common form and a leading cause of visual loss worldwide [**1**].

Treatment might stop or decrease progression in glaucoma, but individual evolution is variable [**2,3**]. In consequence, visual field changes and progression rates differ greatly [**2**].

Many randomized control trials investigated different risk factors in glaucoma progression [**3**]. Based on their results, older age, decreased central corneal thickness (CCT), pseudo exfoliation, lower ocular perfusion pressure, disk hemorrhage, baseline visual field (VF) status and optic nerve anatomy, were variables associated with glaucoma progression. If most reports had a very specific study protocol, with strict research requirements, there is scarce recent data in the literature about glaucoma patients seen in a clinical care context [**4**]. Although retrospective, these types of studies collected relevant information for the clinical practice [**5**].

The aim of our study was to assess the progression rate and risk factors in primary open angle glaucoma, on a clinical care basis.

Materials and Methods

The study was a retrospective review of patient charts.

We studied records of patients with a diagnosis of primary angle glaucoma (POAG) followed in our Glaucoma Unit at "Sf. Spiridon" University Hospital, Iaşi, Romania, between January 2002 and September 2015. Our study was performed while respecting the Declaration of Helsinki. The Ethical Review Board of "Gr. T. Popa" University of Medicine and Pharmacy approved the study and each patient signed an informed consent.

Records were selected only for the patients followed for more than 5 years during the study period. POAG was defined in the presence of open anterior chamber angle on gonioscopy, glaucomatous optic disc damage on clinical examination (focal or diffuse neuroretinal rim thinning, localized notching, or nerve fiber layer defect) and corresponding visual field (VF) defects. Glaucoma severity was graded according to Hodapp criteria [**6**].

VF changes for glaucoma were defined in Standard Automated Perimetry (24-2 SITA Standard SAP, Humphrey Field Analyzer II, Carl Zeiss Meditec Inc., Dublin, CA, USA) if at least two of the three Anderson's criteria were fulfilled (three or more non-edged points in a cluster depressed to $P<5\%$, one of which depressed to $P<1\%$, Glaucoma Hemifield Test outside normal limits and pattern standard deviation depressed to $P<5\%$). Reliability of tests was assessed. Tests with fixation losses, false-positive or false-negative rates >20% were considered unreliable and were excluded from the analysis. A minimum number of 5 VF tests were required for each patient in our study.

All reliable VF tests were analyzed for progression by Glaucoma Progression Analysis (GPA) software, which provided both an event-based and a trend-based progression analysis. Both analyses took the first two reliable VF tests as baseline landmark.

For the purpose of this study, progression was quantitatively assessed by linear regression (Trend) analysis of the mean deviation (MD) changes over time; slopes of progression (decibels/ year) based on threshold maps and its level of significance (p-values) were calculated.

During the study, the patients were followed at every 3-6 months, when identical tests were performed. We excluded patients with significant lens opacities, ocular comorbidities, refractive errors >5D spherical and >3D cylinder.

If both eyes were eligible, only one was chosen based on the worse MD level at baseline. At baseline, clinical parameters such as age, gender, best corrected visual acuity (BCVA) by ETDRS chart, intraocular pressure (IOP) by Goldmann tonometer, central corneal thickness (CCT) by ultrasonic pachymetry (DGH-550, DGH Technology Inc., Exton, PA, USA) C/ D ratio (Volk 78D lens), number of topical medications, VF test parameters, were collected from the charts and included in our study. Also systemic pathologies were checked and noted with

"yes" or "no" if present in the charts (diabetes, arterial hypertension, cardiovascular diseases). At each follow up visit, VA, IOP and VF tests were repeated. Most of the patients required topical therapy, but no surgical intervention (laser or incisional procedure-trabeculectomy) was performed during the follow up period. During monitoring, treatment was modified if the IOP was not efficiently controlled. The IOP level was individually set, according to the glaucoma severity, risk factors, and life span. Intermediary IOP was calculated by averaging all the IOPs taken during the follow up interval. We also calculated the IOP fluctuation based on the standard deviation of intermediary IOP.

Statistical analysis

The data was processed by using the SPSS 18.0 statistical software (SPSS Inc. Chicago, IL, USA). Descriptive analysis was used on demographics; follow up time MD, PSD, and IOP. We also calculated the mean number of VFs/ patient. Progression rate (MD slope) was calculated by linear regression analysis of MD values over time and expressed in dB/ year.

Independent samples t tests were used for comparisons of continuous variables between groups. Wilcoxon test was used to compare paired groups (baseline and final parameters). The association between various risk factors and glaucoma progression was tested by using Pearson Square Chi test. Pearson's correlation coefficients (r) were calculated to assess the relationship between age, BCVA, MD, PSD, IOP, number of medications, IOP fluctuation, CCT, and MD slope. Statistical significance was defined at the $p < 0.05$ level. A logistic regression was used to evaluate the effect of each parameter on the progression outcome. Each parameter was tested independently in a univariate model and then retested after sex adjustment. Analysis of variance (one way ANOVA) was used for comparisons of continuous variables and for building a model of prediction in the visual field decline rate.

Results

We included in our study 121 eyes from 121 patients with open angle glaucoma. Mean age was 61.29 ± 9.48 years, 30 males and 91 females (sex ratio =1: 3). Spherical equivalent (D) was +0.70 ± 1.5. Our follow up period, calculated in months, was 68.81 ± 31.7. All patients were followed with a mean number of VF/ eye = 9.3 ± 2.

Mean central corneal thickness (CCT) in the study was 536 ± 41 μm.

Baseline parameters (visual acuity – VA, intra ocular pressure – IOP, visual field parameters (MD, PSD) are listed in **Table 1**. A significant dynamic was relevant in all measurements ($p<0.05$) except for PSD values ($p>0.05$), when baseline was compared to final levels. Systemic risk factors for our study revealed a high percentage of hypertensive patients (59.8%), 21.4% had positive cardiovascular history and 12% had diabetes mellitus.

Table 1. Comparison of baseline vs. final parameters

Parameter	Baseline	Final	p (t test)
VA (ETDRS)	0.93 ± 0.14	0.88 ± 0.19	**p = 0.01**
IOP (mmHg)	18.20 ±3.77	16.53 ± 2.65	**p = 0.000**
MD (dB)	-3.55 ± 5.19	- 4.87 ± 6.37	**p = 0.000**
PSD (dB)	3.54 ± 2.80	3.84 ± 3.18	p = 0.44

IOP variations are shown in the scheme below (**Fig. 1,2**). At baseline, the mean IOP was 18.20 +/ -3.77 mmHg and decreased significantly during the study. Intermediary IOP was 16.70 +/ -2.53 mmHg, with a significant difference from baseline (p=0.000); final IOP was significantly reduced compared to baseline (16.53 +/ -2.65 mmHg), but no significant "p" could be attributed

when we compared intermediary IOP vs. final IOP. All this IOP reduction was possible under a mean number of 2.01 +/ -1.01 topical substances. Fluctuation of the IOP, calculated based on the standard deviation of intermediary IOP, was 1.86 +/ -4.62 mmHg.

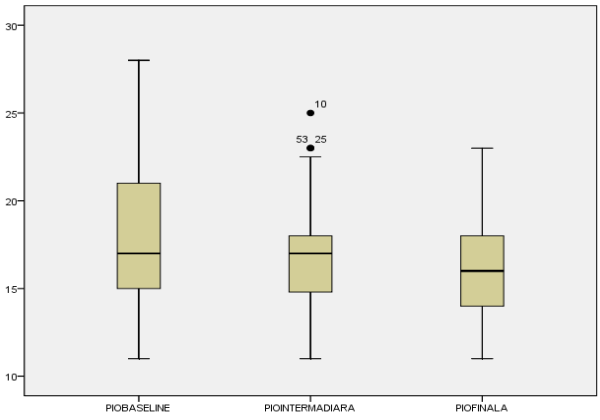

Fig. 1 Mean IOP baseline vs. intermediary vs. final

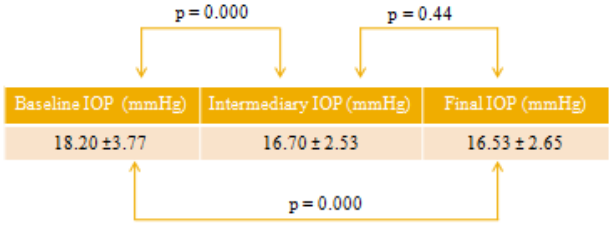

Fig. 2 IOP variations during the study

The visual field decline (MD slope) calculated in our study was -0.21+/ - 0.78 db/ year. Distribution of values showed a Gaussian type of curve (**Fig. 3**); dispersion is presented in **Fig. 4**. As expected, we found positive strong correlations between baseline MD/ final MD, baseline PSD/ final PSD. Strong negative correlations were detected between the generalized reduction of retinal sensitivity at baseline (MD) and focalized visual field defects at baseline (PSD). Final MD/ PSD showed similar high negative correlations. In our study, when the MD slope correlations related to VF parameters were assessed, we found positive high relations with MD at baseline and PSD at baseline. Moreover, the statistical analysis proved a major influence of both parameters over each other (coefficient of determination more than 90%). Based on these findings for our future analysis (predictions) we took into account only the MD baseline value.

Table 2. Correlations between VF parameters

VF parameters correlations	"r"coefficient	p<0.05
MD baseline/ MD final	0.620	p = 0.000
PSD baseline/ PSD final	0.690	p = 0.000
MD/ PSD baseline	- 0.818	p = 0.000
MD/ PSD final	- 0.695	p = 0.000

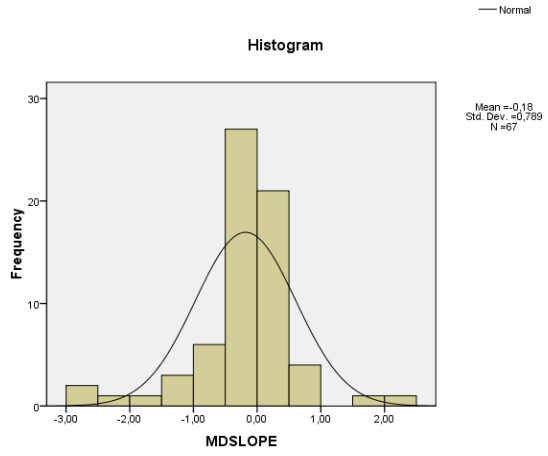

Fig. 3 MD slope histogram

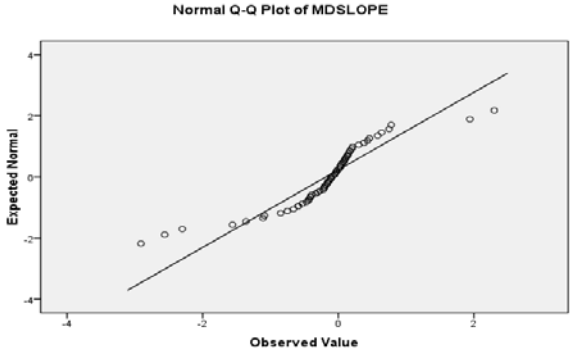

Fig. 4 Normal distribution of MD values in our POAG patients

Other calculated correlations for the MD slope and different parameters showed that males were more prone to a VF decay than women (r=0.194, p=0.04). Yet, the T test showed no statistical difference between sexes when progression rate was analyzed. There was a negative correlation with the MD slope for the IOP level at baseline. Clinically this proved that the higher the IOP at baseline was, the more progression we detected in POAG patients (r=-147, p=0.02). Moreover, the number of topical medications was negatively correlated with the MD slope (r=-198, p=0.03). Practically, this finding meant that progression in glaucoma in our group was connected to the intensity of treatment. In addition, the higher the IOP at baseline was, the more aggressive we treated the patient to reach the "target pressure", individually. We remind at this point that authors changed the medication of patients whenever they considered the optimum IOP was not achieved. Probably this represents the explanation for the fact that IOP fluctuation did not correlate with the MD slope at all (r=-0.100, p=0.25), since changes were made all the way on the study, allowing small variations in IOP that did not impact the progression rate overall. Still, the IOP fluctuation was correlated with the initial IOP level (r=0.820, p=0.001). No other parameters in this study were correlated with the IOP fluctuation. As previously mentioned, the number of topical medications was correlated with the initial IOP level (r=259, p=0.005), with baseline PSD (r=180, p=0.04) and MD slope.

In our study, the thinner cornea was correlated with the MD slope (r=-0.189, p=0.032).

Systemic factors analysis showed that they did not correlate with the VF decline. Age correction did not influence the results, whereas hypertension influenced the progression rate only after sex correction was taken into account. Thus, hypertensive males progress faster than non-hypertensive males (-0.56 db/ year vs. -0.28 db/ year, p=0.05).

Based on these correlations, we could calculate a predictive univariate model (ANOVA) to assess which factors affect more the visual field decay in our study patients. Results are summarized in **Table 3**. For this study, the baseline parameters (MD, IOP) alltogether with the number of topical substances and a thin cornea seemed to predict the visual field decay in a large proportion (71.7%).

Table 3. ANOVA – Model Summary

ANOVA - Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	,355[a]	,126	,113	,74283	,126	9,385	1	112	,003
2	,810[b]	,556	,545	,46956	,530	96,671	1	112	,000
3	.841[c]	,635	,612	,53591	,584	97,216	1	112	,000
4	.862[d]	,717	,703	,36517	,489	98,552	1	112	,004

a. Predictors: (Constant), MD baseline

b. Predictors: (Constant), PIO baseline, MD baseline

c. Predictors: (Constant), MD baseline, PIO baseline, nr. medicamente

d. Predictors: (Constant), MD baseline, PIO baseline, nr. medicamente, CCT

e. Dependent Variable: MD slope

Discussions

The progression rate and risk factors are among the most important aspects in glaucoma care, because of their impact upon visual decay. Although several guidelines for glaucoma management recommended the assessment of progression rate in routine care [**6**], information

was scarce until recently [**7,8**]. Based on these studies, older age, baseline IOP, decreased CCT, pseudoexfoliation, baseline VF status or systemic diseases (hypertension, diabetes, cardiovascular events) were risk factors associated with the VF progression [**8**].

Our study tried to prove that on clinical care grounds, progression in open angle glaucoma and its risk factors might be different than in standard clinical trials possibly due to standardized inclusion/ exclusion criteria, strict treatment plans, clear visit schedule.

Our patients (121 eyes) with primary open angle glaucoma were followed on clinical care grounds. Overall, in our study, the visual field declined at a rate of -0.21 dB/ year. This is much lower than the other reported results, no matter if randomized control trials or clinical care studies are evaluated [**7-11**]. Still, the mean age of our patients was younger than in all the other studies and based on this younger age in our study group, we decided to treat the patients more aggressively from the start, assuming a longer life span.

There was no standard IOP lowering strategy in our study, meaning that each doctor involved in the study decided how/ when to adjust the IOP according to his own experience, until the desired level was reached. No additional surgical procedure was recorded in any patient along the follow up period, but only changes in the topical treatment.

Our results showed that the visual field decay (MD slope) was correlated with baseline MD, baseline IOP and number of topical substances. In addition, a thin CCT was a risk factor in progression in our study. Based on these correlations, a univariate analysis allowed us to create a model of prediction in POAG progression. Thus, all the above-mentioned parameters seemed to predict de visual field deterioration in a proportion of 71.7%. In this aspect, our results were similar to the OHTS [**12**] or EMGT study [**3**].

EMGT results showed that, by reducing the IOP with 25%, progression occurred later than in non-treated patients. This could have also been the reason for our patients progressing at such a low rate compared to other studies, since medication was constantly changed/ added to lower the IOP according to the concept of "target pressure".

Most randomized control trials failed to show any association between sex and glaucoma progression [**3,13,14**]. In the OHTS [**15**], men were more likely to convert to glaucoma than women. No differences were found in our study regarding the progression rates by Wilcoxon test ($p>0.05$).

A recent meta-analysis presented data on systemic hypertension [**16**], cardiovascular diseases [**16**] and diabetes [**17,18**] as risk factors in glaucoma. A systolic pressure lower than 125 mmHg was a risk factor for progression in EMGT [**3**], whereas there was no association between systemic hypertension and OAG progression in AGIS [**17**] and CNGTS [**19**]. Recently, a more balanced opinion was offered, stating that systemic hypertension had a different effect on the development/ progression in glaucoma in different age groups [**17,18**].

In our study, after statistical corrections, we found that hypertensive males progressed at a higher rate than non-hypertensive males. We used trend analysis to define and measure progression rates (db/ year) in the same manner as Nouri-Mahdavi [**20**] evaluated some of the patients in AGIS. We acknowledged that the progression rate might not have been linear in glaucoma patients, especially for those followed on long term, but this approach allowed the clinician to evaluate the patient's behavior when a certain treatment was applied. Yet, in our study, both the follow up period and the number of VF were comparable with other studies [**21,22**], so the calculated MD slope could be considered reliable.

Declaration of interest (financial disclosure)

Authors declare none.

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