Long Term Results of Visual Field Progression Analysis in Open Angle Glaucoma Patients Under Treatment

Tolga Kocatürk[*,1], Sinan Bekmez[1], Merve Katrancı[2], Harun Çakmak[1] and Volkan Dayanır[1]

[1]*Department of Ophthalmology, Faculty of Medicine, Adnan Menderes University, Aydın, Turkey*

[2]*Department of Biostatistics, Faculty of Medicine, Adnan Menderes University, Aydın, Turkey*

Abstract: *Purpose*: To evaluate visual field progression with trend and event analysis in open angle glaucoma patients under treatment.

Materials and Methods: Fifteen year follow-up results of 408 eyes of 217 glaucoma patients who were followed at Adnan Menderes University, Department of Ophthalmology between 1998 and 2013 were analyzed retrospectively. Visual field data were collected for Mean Deviation (MD), Visual Field Index (VFI), and event occurrence.

Results: There were 146 primary open-angle glaucoma (POAG), 123 pseudoexfoliative glaucoma (XFG) and 139 normal tension glaucoma (NTG) eyes. MD showed significant change in all diagnostic groups ($p<0.001$). The difference of VFI between first and last examinations were significantly different in POAG ($p<0.001$), and XFG ($p<0.003$) but not in NTG. VFI progression rates were -0.3, -0.43, and -0.2 % loss/year in treated POAG, XFG, and NTG, respectively. The number of empty triangles were statistically different between POAG-NTG ($p=0.001$), and XFG-NTG ($p=0.002$) groups. The number of half-filled ($p=0.002$), and full-filled ($p=0.010$) triangles were significantly different between XFG-NTG groups.

Conclusion: Functional long-term follow-up of glaucoma patients can be monitored with visual field indices. We herein report our fifteen year follow-up results in open angle glaucoma.

Keywords: Glaucoma, normal tension, progression, primary open-angle, pseudoexfoliation.

INTRODUCTION

Glaucoma is a progressive optic neuropathy leading to retinal ganglion cell loss, optic nerve atrophy, and visual field (VF) loss. It is a worldwide disease with most patients having VF loss at the time of diagnosis. Since glaucomatous damage is irreversible, early diagnosis and monitoring of progression become important in management [1].

Glaucomatous damage is often evaluated with ophthalmic examination, VF test, optic disc photography and retinal nerve fiber layer imaging. Primary open-angle glaucoma (POAG) is the most common type of primary, and pseudoexfoliative glaucoma (XFG) is the most common type of secondary high tension open angle glaucoma. In patients with XFG, VF loss and optic nerve damage occur faster than POAG patients [2,3]. Normal tension glaucoma (NTG) being the second most common type of open angle glaucoma, also known as low tension glaucoma, is defined by glaucomatous VF loss with glaucomatous optic nerve damage in the presence of normal intraocular pressure (IOP) measurements.

The originality of this study is to investigate the visual field progression in terms of both event and trend analysis with the aid of computerized VF testing. In our study, we aimed to characterise progression characteristics of the three most common types of open angle glaucoma; namely POAG, XFG, and NTG that were under medical treatment at a glaucoma clinic.

MATERIALS AND METHODS

Glaucoma patients who were followed-up at Adnan Menderes University, Department of Ophthalmology, Glaucoma Clinic between 1998 and 2013 were analyzed retrospectively. The study protocol had the approval of the university's ethics committee and complied with the guidelines set forth in the Declaration of Helsinki.

Inclusion criteria were an age of ≥18 years, glaucomatous optic nerve damage, glaucomatous VF defect, open angles on gonioscopy, detailed ophthalmologic examination three times in a year and VF tests done with Humphrey Visual Field Analyzer (Humphrey Systems Field Analyzer Model II 750, Zeiss, USA) using 24-2 Swedish Interactive Threshold Algorithm. If the patient was on medication at the time of application to our glaucoma clinic then a proper washout period was allowed before scheduling the office hours diurnal IOP measurement.

All IOP measuements were done by Goldmann Applanation Tonometry (GAT). All patients had an office hours diurnal IOP measurement taken at morning, noon and evening during a single day while not on antiglaucoma medication.

*Address correspondence to this author at the Department of Ophthalmology, Faculty of Medicine, Adnan Menderes University, Aydın, Turkey; Tel: 00 90 533 344 41 11; Fax: 00 90 256 214 64 95; E-mail: tolgakocaturk@gmail.com

Exclusion criteria included presence of narrow angle, history of angle closure glaucoma crisis, ocular (corneal opacity, diabetic retinopathy, macular pathologies, retinal vascular occlusions, ptosis), and cranial pathologies that can affect visual field test results.

POAG was diagnosed in the presence of glaucomatous disc cupping, glaucomatous VF defect, open angles and an IOP of ≥21mmHg on one or more office hours diurnal IOP measurement. In case of XFG, the only difference from POAG was the presence of pseudoexfoliative material at the pupillary edge and/or on the anterior lens capsule. In order to establish the diagnosis of NTG, all the office hours diurnal IOP measurements must have been <21 mmHg (with no single measurement >24 mm Hg) [4]. Mean "follow-up IOP" was obtained by taking the average of IOP measurements in every follow-up visit. Pachymetry measurements (Heidelberg Engineering IOPac; Starfish, Product Engineering Inc., Victoria, Canada) were recorded when available.

Medical treatment started with a single agent with the aim of getting a drop of at least 20% in IOP. If the IOP response was inadequate, we either switched to a new agent or added on a new agent depending on the response to the first agent [5]. Hence, the results presented show the number of antiglaucomatous agents, not antiglaucomatous boxes. In case of inadequate IOP control with maximum medical therapy and/or visual field progression, surgical options were discussed.

VF indices recorded were VFI and MD at the first (VFI first, MD first), and last (VFI last, MD last) visits. Trend analysis was obtained from the rate of progression of visual field index (percent change per year, %/year). Event analysis was done by counting the number of empty triangles, half-filled triangles, and full-filled triangles at the last follow-up VF. Data were obtained from Glaucoma Progression Analysis software of Humphrey Visual Field Analysis. Tests having fixation loss more than 30%, false negative more than 20% or false positive more than 20% were excluded. Follow-up visits with complete ophthalmologic exam and VF test were scheduled every 4 months.

Statistical Analysis

Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. To compare normally distributed independent variables between groups One Way Analysis of Variance test was used. Descriptive statistics for normally distributed variables central corneal thickness, and IOP are presented as mean±standard deviation. Kruskal Wallis test was used to compare non-normally distributed independent variables between groups. Wilcoxon test was used to compare the non-normally distributed dependent variables. Descriptive statistics for non-normally distributed variables MD, VFI, rate of progression, follow-up years, and number of triangles are presented as median (25-75 percentiles). To analyse the categorical data, a Chi-square test was used, and descriptive statistics are presented as frequency (%). p values below 0.05 were considered as statistically significant.

RESULTS

408 eyes of 217 patients of which 103 (47.5%) were men and 114 (52.5%) were female were analyzed. There were no statistically significant differences in terms age, sex, family history of glaucoma and follow-up time between groups (Table **1**). Corneal thickness was the highest in POAG group and the lowest in NTG, and follow-up IOP was the longest in XFG and lowest in NTG, the differences being satistically significant (p<0.001).

Table 1. Demographic data, pachymetry and follow-up of all diagnostic groups.

	POAG (n=146)	XFG (n=123)	NTG (n=139)	p
Age (year)	68±6	70±7	66±8	0.254
Female (%)	38 (%51)	36 (%51)	40 (%56)	0.736
Family history	16 (%21)	9 (%13)	16 (%23)	0.260
Follow-up (year)	7.6±2.6	6.5±4.5	7.4±2.5	0.397
Pachymetry (μm)	544±35	539±35	530±31	<0.001
Follow-up IOP (mmHg)	15±2	17±3	12±1	<0.001

The average number of antiglaucomatous agents used to reach the target IOP level were 2.2, 2.8, and 1.4 in POAG, XFG, and NTG groups, respectively. There was statistically significant difference between groups in terms of average number of antiglaucoma agents used (p=0.002).

Table 2. MD, VFI and rate of progression values (25-75 percentiles) for diagnostic groups.

	POAG	XFG	NTG
MD first	-3.05 (-5.40-[-1.90])	-6.93 (-14.90-[-2.86])	-2.55 (-4.59-[-1.40])
MD last	-3.85 (-6.55-[-2.48])	-8 (-17.45-[-4.48])	-3.50 (-7.14-[-2.04])
VFI first	94 (87-97)	85 (52-96)	93 (88-97)
VFI last	92 (82-97)	82 (47-94)	95 (87-98)
Rate of progression (% loss/year)	-0.3 (-0.78-[-0.05])	-0.43 (-1.05-[-0.15])	-0.2 (-0.66-[-0.05])
P value of MD first/last	<0.001*	<0.001*	<0.001*
P value of VFI first/last	<0.001*	0.003*	0.962

MD first/last: Mean Deviation at the first ophthalmologic examination and the last follow-up.
VFI first/last: Visual Field Index at the first ophthalmologic examination and the last follow-up.
*: Statistically significant.

VF indices at the first and last examinations are summarized in Table **2**. MD decreased significantly in all groups. VFI decreased significantly in all groups except NTG where there was an increase which was not found to be statistically significant.

Comparison of MD, VFI and rate of progression between groups showed that XFG eyes had significantly worse MD and VFI values compared to POAG and NTG eyes both at the first and last visit (Table **3**). Rate of progression was found to be significantly faster only in the XFG-NTG comparison.

Table 3.   P values for pairwise comparison of MD, VFI, rate of progression in diagnostic groups.

	POAG-XFG	**POAG-NTG**	**XFG-NTG**
VFI first	0.023*	1.000	0.011*
MD first	0.002*	0.385	<0.001*
VFI last	0.036*	0.123	<0.001*
MD last	0.001*	1.000	<0.001*
Rate of progression	0.340	0.554	0.015*

*: Statistically significant.

The numbers of "empty triangle", "half-filled triangle" and "full-filled triangle" in the last visit are shown in Table **4**. The number of empty triangles is statistically different between XFG-NTG (p=0.002), and POAG-NTG (p=0.001) groups. A number of half-filled (p=0.002) and full-filled (p=0.010) triangles were statistically different between XFG-NTG groups (Table **5**).

Table 4.   Number (25-75 percentiles) of "empty triangle", "half-filled triangle", and "full-filled triangle" in the last visit for each diagnostic group.

	POAG	**XFG**	**NTG**
Empty triangles	4 (2-6)	4 (2-5)	2 (1-4)
Half-filled triangles	1 (0-2)	1 (0-3)	1 (0-1)
Full-filled triangles	1 (0-1)	1 (0-3)	0 (0-1)

Table 5.   P values of diagnostic group comparisons for "empty triangle", "half-filled triangle", and "full-filled triangle".

	POAG-XFG	**POAG-NTG**	**XFG-NTG**
Empty triangles	1.000	0.001*	0.002*
Half-filled triangles	0.486	0.109	0.002*
Full-filled triangles	0.106	1.000	0.010*

*: Statistically significant.

The distribution of eyes according to progression rate is plotted in Fig. (**1**). About half of the eyes in each group had a progression in the range of -0.8 to -0.1 %loss/year; 48% in POAG, 63% in XFG, and 52% in NTG. About a quarter of the eyes had worse progression than -0.8 %loss/year both in

POAG (25%) and XFG (31%), but this number was less in NTG (14%). One tenth of the eyes in POAG (11%) and NTG (9%) did not show any progression which was less seen in XFG (4%). There were also a significant proportion of eyes showing improvement in all groups but especially in NTG (24%).

DISCUSSION

Functional long-term follow-up of glaucoma patients can be monitored with event and/or trend analysis of visual field parameters. In our study, NTG had the lowest median progression rate in trend analysis (-0.2 %loss/year), while XFG had the highest (-0.43 %loss/year) (p=0.015). There is also considerable variation in terms of progression seen in trend analysis within the same diagnostic group. In our study this range for POAG, XFG, and NTG were -24.20 to 4.80, -7.50 to 2.10, and -12.40 to 3.10, respectively. As such, customized evaluation for each eye becomes a necessity.

Progressive visual field loss, thinning of the retinal nerve fiber layer, IOP elevation (except NTG) are seen as common clinical features in all of these diseases that we gather under the term of glaucoma. But medical and/or surgical treatment requirements and progression rates vary considerably among different diagnostic groups as well as patients. Heijl *et al*. [6] found mean progression rates of -1.31, -3.13, and -0.36 dB/year in untreated high-tension glaucoma, XFG, and NTG respectively. Anderson *et al*. [7] found the mean progression rate of -0.41 dB/year for untreated NTG patients. For treated NTG patients the progression rates were reported to vary from -0.1 to -0.35 dB/year [8,9]. Sakata *et al*. [10] reported a rate of change in the MD value of -0.16±0.31 dB/year for NTG patients who were receiving only medical treatment over 5 years. De Moraes *et al*. [11] reported the highest mean progression rate of -0.65 dB/year for XFG eyes among all glaucoma subtypes under treatment. The VFI progression rates that we had found were -0.3, -0.43 and -0.2 %/year in the treated POAG, XFG and NTG patients, respectively. In general if we take 1% loss as 0.3 dB loss then the mean VFI progression rates could roughly be calculated [12].

Ahrlich *et al*. [13] compared the differences in visual field progression of 154 eyes with XFG and 139 eyes with NTG. As in the present study, Ahrlich *et al*. [13] found a greater values for the mean IOP (17±3 mm Hg *vs* 13±2 mm Hg, p < 0.01) and for the mean pachymetry in the XFG group (544±36 μm *vs* 533±36 μm, p=0.01). NTG patients were younger than those with XFG (73±9 years *vs* 63±13 years, p < 0.01). Ahrlich's study reported progression of MD, whereas the current study reports progression of VFI. They found statistically significant difference almost twice as much as in the mean value of rate of progression of MD in XFG group (-0.64±0.7 dB/year) compared to the NTG group (-0.35±0.3 dB/year). This difference was found to be nonsignificant, after adjusting for age, mean IOP, and CCT. They reported that progression in NTG patients was seen in the central VF more often, independent of other factors [13].

Progression risk of glaucoma is increased by age and severity of damage [14,15]. Bengtsson *et al*. [16] reported that VFI provides age-corrected visual function and functional glaucomatous progression by using linear regression analysis. However, in our study, there were no
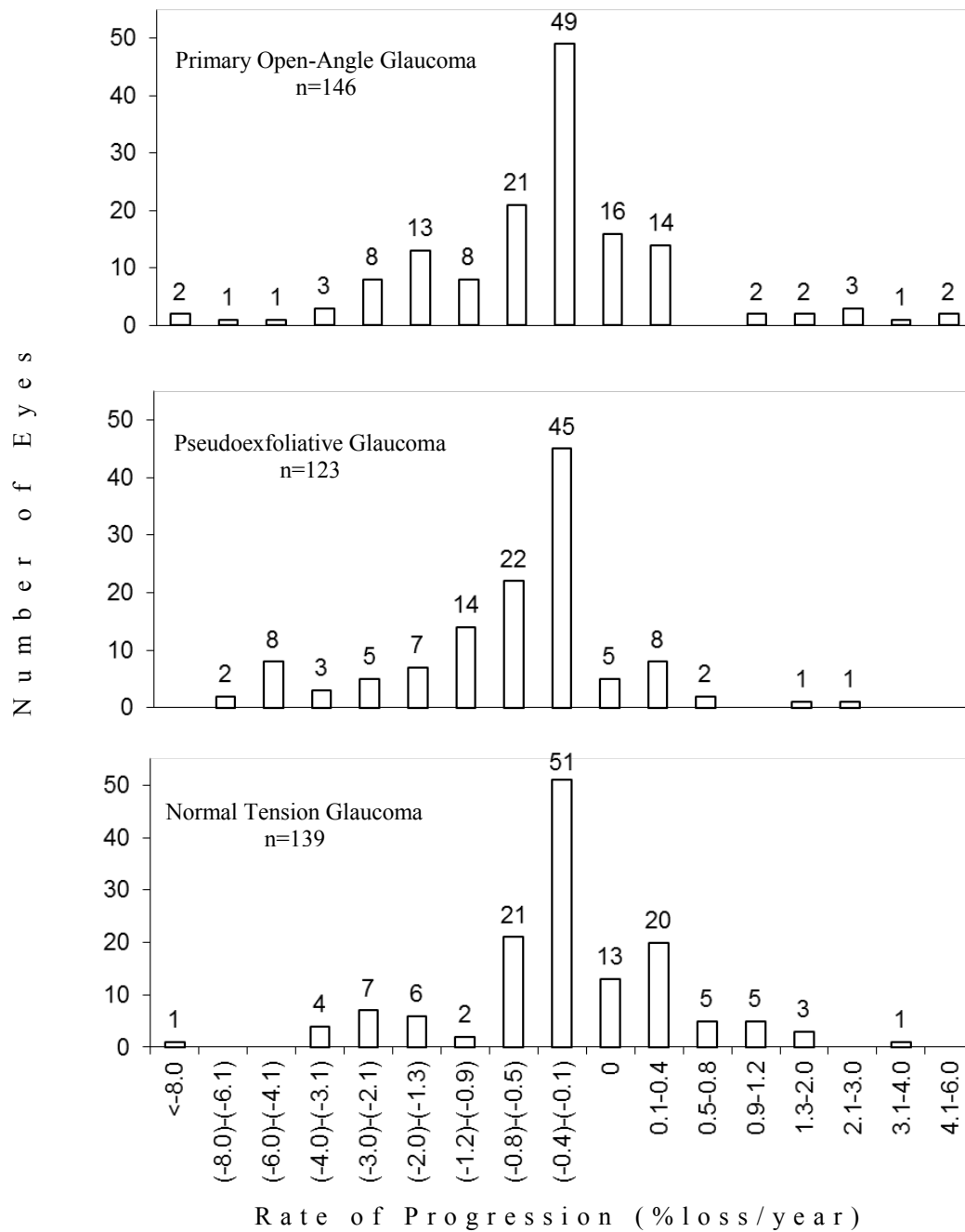
Fig. (1). The distribution of rate of progression values in each diagnostic group. The intervals used in horizontal axis are not linear and the range is increasing as it gets farther from zero.

statistically significant differences between groups in terms of age, although the highest average age of 70 was found in the XFG group supporting the argument that XFG arises later in life.

CONCLUSION

1. With the ever increasing average life expectancy, long-term follow-up and treatment plans become more important in progressive and chronic diseases like glaucoma.

2. Progression rates can differ between patients within the same diagnostic group and between diagnostic groups.

3. Although there was no statistically significant difference in progression rate between NTG and POAG groups; NTG patients had a lower progression rate compared to the other diagnostic groups.

4. The progression rate for XFG seemed to be a little bit higher than POAG but there was no statistically significant difference. However, XFG patients needed significantly more anti glaucoma agents to reach the target IOP.

5.   We believe that long-term progression of glaucoma patients should be closely monitored and treatment should be individualized with reference to VF progression results.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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