

The rates of visual field progression in glaucoma and its clinical importance

Taxas de progressão do campo visual em glaucoma e sua importância clínica

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ABSTRACT

The rate of visual field progression is an essential factor in determining risk of visual disability or blindness in glaucoma patients. Knowledge of the rate of progression of a particular patient, in combination with an estimation of their longevity and other clinical factors, allows clinicians to optimize management by providing appropriately aggressive treatment. Despite decades of research on the treatment of glaucoma, the natural history of glaucomatous visual field progression in untreated and treated patients remains unclear. The purpose of this review is to provide a comprehensive summary of the literature surrounding the rate of visual field progression in glaucoma. Most of the available data pertains to primary open angle glaucoma, but we will also review progression rates in other subtypes of open angle glaucoma, such as pseudoexfoliative glaucoma and normal tension glaucoma, as well as in primary angle closure glaucoma. Specifically, we will cover methods to identify rates of progression, rates of progression in treated versus untreated patients, factors that may influence progression, and lastly, suggest some parameters that might help clinicians in determining acceptable rates of visual field deterioration in patients with glaucoma.

RESUMO

A taxa de progressão do campo visual é um fator essencial para determinar o risco de incapacidade visual ou cegueira em pacientes com glaucoma. Conhecer a taxa de progressão de um determinado paciente, em combinação com uma estimativa de sua longevidade e outros fatores clínicos, permite que os médicos otimizem a conduta, fornecendo um tratamento adequadamente agressivo. Apesar de décadas de pesquisa sobre o tratamento do glaucoma, a história natural da progressão do campo visual glaucomatoso em pacientes não tratados e tratados permanece pouco clara. O objetivo desta revisão é fornecer um resumo abrangente da literatura sobre a taxa de progressão do campo visual do glaucoma. A maioria dos dados disponíveis diz respeito ao glaucoma de ângulo aberto primário, mas também revisaremos as taxas de progressão em outros subtipos de glaucoma de ângulo aberto, como o glaucoma pseudoexfoliativo e o glaucoma de tensão normal, bem como o glaucoma primário de ângulo fechado. Especificamente, iremos cobrir métodos para identificar taxas de progressão, taxas de progressão em pacientes tratados versus não tratados, fatores que podem influenciar a progressão e, finalmente, sugerir alguns parâmetros que podem ajudar os médicos a determinar taxas aceitáveis de deterioração do campo visual em pacientes com glaucoma.

CLINICAL IMPORTANCE OF MEASURING RATES OF VISUAL FIELD PROGRESSION

Glaucoma is an acquired neurodegenerative optic neuropathy characterized by progressive optic nerve changes with corresponding visual field deficits. As the most common cause of irreversible blindness in the world, glaucoma can pose a substantial negative impact on patients' quality of life (QoL).⁽¹⁾

Since glaucoma is typically an insidious disease with few, if any, clinical symptoms in its early stages, screening patients is essential for early disease detection. Assessment for glaucoma involves careful examination of the optic nerve, which can be aided by objective assessment with imaging tools, such as optical coherence tomography (OCT), and perimetric evaluation to determine the presence of visual field defects. In addition, one must perform a thorough clinical examination, including measurement of intraocular pressure (IOP), gonioscopy and slit lamp evaluation to identify secondary causes of glaucoma. Intraocular pressure is the only modifiable risk factor that has been shown to slow or halt the progression of glaucoma.⁽²⁻⁴⁾ However, patients can still progress despite significant reduction of IOP. Therefore, clinicians must pay close attention to signs of visual field and/or structural deterioration, even in the presence of well controlled IOP.

Given the progressive nature of glaucoma, it is expected that patients will exhibit some deterioration of their visual field over long periods of time. Yet, there is a paucity of long-term data in the literature regarding the disease trajectory in treated patients. Nonetheless, a retrospective review of patients followed at the Mayo Clinic identified that at 20 years follow-up, 27% of patients suffered legal blindness in one eye, and 9% were blind in both eyes.⁽⁵⁾ Studies have shown that the rate of progression varies significantly among treated patients with glaucoma.^(6,7) As such, identification as early as possible of patients progressing at a fast pace, in combination with an estimation of their longevity, allows a clinician to optimize management by providing appropriately aggressive treatment to those with high rates of progression, and sparing those with low rates of morbidity to unnecessary treatment.⁽⁸⁾ Thus, the rate of disease progression is an essential factor in determining risk of visual disability or blindness in glaucoma. Like other chronic neurodegenerative diseases, the goal of glaucoma therapy should not be to avoid any disease progression in the long term, but rather to prevent significant visual impairment and decreased vision-related QoL due to glaucoma progression.

The purpose of this review is to provide a summary of the literature surrounding rates of visual field progression in glaucoma. This review will focus on primary open angle glaucoma (POAG), but we will also comment on progression in primary angle closure glaucoma (PACG), normal tension glaucoma (NTG), and other common types of secondary open angle glaucoma, such as pseudoexfoliative glaucoma (PXG). Specifically, we will cover methods to identify rates of progression, compare rates of progression in treated versus untreated glaucoma, identify factors that may influence progression, and lastly, suggest some parameters that might help clinicians in determining acceptable rates of visual field deterioration in glaucoma patients.

METHODS TO IDENTIFY VISUAL FIELD PROGRESSION

Since longitudinal perimetric testing continues to be the mainstay for assessing progression of glaucoma, it is important to have methods to objectively determine visual field progression. Currently, standard 'white-on-white' automated visual field testing remains the most utilized method to assess visual fields. The Humphrey perimeter (Carl Zeiss Meditec, Dublin, California, United States) and the Octopus perimeter (Haag Streit AG, Koeniz, Switzerland) are the most frequently used devices in clinical care and research studies. Data produced by the machines are numeric and the sensitivity ranges of these tests are capable of capturing glaucoma progression. However, many factors can confound the accurate detection of progression in glaucoma: test results can be quite variable, related to patient inattentiveness, poor performance or inherently inconsistent results particularly for regions of the visual field that are abnormal; other frequent pathologies, such as media opacities from cataract or corneal disease, as well as retinal pathology, can influence the results. As such, accurate detection of glaucomatous visual field progression can be challenging.

Qualitative assessment of visual field progression based on subjective comparison of series of visual fields has been found to be very unreliable, with poor inter-observer agreement, even among glaucoma experts.⁽⁹⁾ Therefore, computer-based algorithms have been developed to optimize detection of visual field progression. The main goal of these algorithms is to account for variability in visual field tests, which may otherwise be challenging for a clinician.

Methods to assess visual field progression can be classified as event-based and trend-based analysis. In simple

terms, event-based analysis asks the question “Has the visual field defect progressed at this point in time?” by comparing a current visual field test to a baseline test. In general, event-based analysis defines progression if a global index or a defined number of test locations show decreased sensitivity that exceeds a predefined prediction limit of variability.⁽¹⁰⁾ Trend-based analysis asks the question: “What is the rate of progression of the disease up to this point in time?”. It determines how fast the disease is progressing by performing regression analyses on all the available tests and provides estimates of the rate of change, usually described as loss or progression per year.

The event-based analysis software that is more frequently used in clinical practice is the glaucoma progression analysis (GPA), which was developed from criteria utilized in the Early Manifest Glaucoma Treatment (EMGT) trial. The GPA compares each test result, point by point, with values from two averaged baseline tests. Points are highlighted on a probability plot if changes exceed the typical measurement variability derived from a group of patients with stable glaucoma. If such changes occur at three or more points and in two consecutive follow-up tests, the GPA raises an alert of “possible progression”; if they occur in three consecutive tests, an alert of “likely progression” is raised.⁽¹¹⁾ Event-based analysis, given its roots in glaucoma landmarks trials, is most useful when the goal is to determine if a certain therapy can reduce the number of patients reaching an endpoint of visual field progression over a certain period of time.

However, in clinical practice, it has been suggested that trend-based analysis may be more beneficial when monitoring patients over a long period of time, when the main goal is to determine the risk of patients progressing to significant visual disability. In that kind of scenario, the rate, or how fast, progression is occurring is critical to inform clinical decisions.

Global indices, such as mean deviation (MD) and pattern standard deviation (PSD) have been used to estimate the global rate of progression of visual field. MD refers to the difference in the patient's visual field sensitivities compared to those expected from the age-matched normative database, presented in decibels (dB).

The MD index (MDI) expresses the slope of a simple linear regression analysis of MD values over time. Because a normal eye has an MD value of 0dB and a blind glaucoma eye has an MD value of less than 25 to 30dB, depending on age, an eye would progress from normal to blind in approximately 25 to 30 years if the rate of progression was 1dB/year, while an eye with a more rapid progression

rate of 2.5dB/year would decline from normal to blind in 10 to 12 years. Since MD can be affected by media opacity, significant cataract formation can affect assessment of glaucoma progression with MDI.^(12,13)

Another global parameter commonly utilized to estimate rate of progression is the visual field index (VFI). Visual field index assigns a number between 1% and 100% based on aggregate percentage of visual function, with 100% being a perfect age-adjusted visual field. Unlike MDI, central visual field points are more heavily weighted, and the percentage of visual field loss is calculated based on the depth of loss according to total or pattern standard deviation. After a minimum of five visual field tests are completed, the VFI values are plotted as a function of the patient's age. The rate of progression can be derived (percentage of VFI loss per year) and extrapolated to help guide clinical decisions. Compared to MDI, some studies suggest VFI is less affected by cataract development and cataract surgery.⁽¹⁴⁾ Yet, VFI has been associated with issues with discontinuity at advanced stages of loss and can also miss early diffuse visual field damage due to a ceiling effect.⁽¹⁵⁾

Several studies have compared event-based analysis such as GPA with trend-based analysis using VFI or MDI in their sensitivity and specificity to detect visual field progression. These studies are somewhat plagued in that we do not have an independent, validated, and objective marker of disease progression in order to assess the sensitivity and specificity of these methods. Another consideration is that the definition of progression for trend-based analysis is not uniformly accepted, with progression being defined as any slope that is significantly different than zero or any other minimal slope value defined in the study. Notwithstanding these limitations, studies tend to show that GPA may detect progression earlier, however, with longer follow-up or individuals with more advanced disease, trend-based analysis tend to detect a larger number of progressing cases.^(16,17) In a study that rigorously controlled for specificity by using a simulation technique, Wu and Medeiros showed similar sensitivity in detecting progression between GPA and trend-based analysis, utilizing VFI or MDI.⁽¹⁸⁾ Studies have also showed only fair to moderate agreement between event-based and trend-based analysis, suggesting that both methods offer complementary information on progression, and could be combined in clinical practice.^(16,17)

In patients followed for longer periods of time, event-based analysis can become less relevant, and trend-based analysis might provide a more accurate information of what

statistic and uses a permutation analysis to present a p-value for overall change using only the patient's own data. Since these different methods are not yet widely utilized in clinical practice, we will not expand on their utility in this article.

RATES OF CHANGE IN UNTREATED GLAUCOMA (NATURAL HISTORY)

Given the progressive nature of glaucoma, therapy is usually instituted without delay in newly diagnosed patients and, therefore, there is limited information in the literature regarding rates of visual field progression in untreated glaucoma.

Nonetheless, the few prior studies on this topic provide meaningful information on the natural history of glaucoma.

The Collaborative Normal-Tension Glaucoma Study (CNTGS) described the effect of IOP lowering therapy on visual field progression in NTG patients with high risk for progression. In this study, patients with NTG were observed until they showed confirmed visual field or optic disc progression, or a new optic disc hemorrhage (ODH). At that point, they were randomized to IOP lowering therapy or observation, except for patients enrolled with visual field defects threatening fixation, who were randomized right away. The natural history of NTG was assessed by evaluating the visual field data from patients randomized to observation, in combination with data from all patients prior to randomization and with data from patients who were never randomized, since they never showed confirmed progression. The authors reported that only approximately half of the patients showed visual field progression within five to seven years. The mean progression rate in this untreated cohort of NTG patients was -0.41dB/year .⁽²¹⁾

The EMGT trial randomized patients with open angle glaucoma, including POAG, NTG and PXG, to IOP reduction or an untreated control arm to evaluate the effects of IOP reduction in open angle glaucoma. After a median follow-up of 6 years, progression was less frequent in the treatment group (58/129; 45%) than in controls (78/126; 62%) and occurred significantly later in treated patients.⁽¹¹⁾ Among untreated patients, the median rates of visual field loss were -0.40dB/year overall, with large differences between the subtypes of open angle glaucoma (-0.22dB/year in NTG, -0.46dB/year in high tension glaucoma and -1.13dB/year in PXG).⁽⁷⁾

Perhaps the only placebo-control trial on the effect of IOP lowering on visual field preservation in glaucoma was

conducted by Garway-Heath et al.⁽²²⁾ This triple-masked, multicenter trial enrolled newly diagnosed glaucoma patients who were randomized to topical latanoprost or placebo. Visual field preservation was significantly longer in the latanoprost group compared to the placebo group, with an adjusted hazard ratio of 0.43.⁽²²⁾ The rate of visual field change was significantly faster in the placebo group when compared to the treatment group (-0.29dB/year versus $+0.03\text{dB/year}$).⁽²³⁾

RATES OF VISUAL FIELD CHANGE IN TREATED GLAUCOMA

Several studies have investigated the rate of visual field progression in treated glaucoma patients, with a large variability of the reported average rate of change among the various studies. It is worthwhile reviewing some of the large studies that reported progression rates in treated glaucoma, as this information can help us determine the expected average rate of change in patients under active care, which can guide us in determining clinically meaningful rates of change.

A large Swedish retrospective chart review study on 583 patients with POAG and PXG with at least five visual fields showed that after a mean follow-up of 7.8 years (average of 8.9 visual fields per patient) the mean rate of change was -0.80dB/year , with a small subset of patients (5.6%) having a rate worse than 2.5dB/year .⁽²⁴⁾ A similar, multicenter, non-interventional cohort study performed in France included 228 patients (441 eyes) followed for at least six years. After a mean follow-up of 8.4 years (average of 18.4 visual fields per patients) the rate of change was -0.09dB/year in ocular hypertensives, -0.32dB/year in early POAG and -0.54dB/year in advanced POAG.⁽²⁵⁾ A UK study reported on the rate of glaucoma progression among 2208 patients with POAG and OHT followed in secondary care settings, as opposed to tertiary settings. In this cohort, the median rate of progression was -0.1dB/year over a median of 6.7 years, with 477 (21.2%) progressing at greater than -0.5dB/year and 46 (2.1%) progressing at greater than -2.0dB/year . Interestingly, of those with a final MD worse than -10dB in their better eye, 14.0% were 'fast progressors' (greater than -2dB/year), 33.7% 'moderate progressors' (-1 to -2dB/year), and 28.8% 'slow progressors' (-0.3dB to -1dB/year).⁽²⁶⁾

Our group reported on rate of change in 2,324 patients with glaucoma or ocular hypertension with at least five visual field examinations monitored in a tertiary care setting. After a median follow-up of 7.1 years

(eight examinations per patient), the median MD rate was -0.05dB/year , with 4.3% classified as “fast progressors” (-1 to -2dB/year) and 1.5% as “catastrophic progressors” (worse than -2dB/year). Even considering only patients in the worse tertile in terms of baseline MD (mean MD of -7.79 dB), the median MD rate was only -0.12dB/year , but a larger percentage of patients were classified as “fast progressors” (8.9%) and “catastrophic progressors” (2.9%).

Tables 1 and 2 summarize pertinent studies that reported on rates of progression in treated and untreated glaucoma patients. Only studies that expressed an MDI or VFI rate of annual progression were included in the table. The range of MD change was between -1.08dB/year and -0.29dB/year among untreated patients and between -0.88dB/year and $+0.03\text{dB/year}$ among treated patients. The large variability in reported rate of

change is likely related to differences in the baseline visual field damage, mean age of patients, types of glaucoma, length of follow-up and mean level of IOP during follow-up. Moreover, there is significant variability of study types, with some being prospective randomized control trials, while others are retrospective cohorts. There is also great variability within each study on the rates of progression of treated patients, evidenced by the large standard deviation of the mean rates of the various studies. An overall conclusion that can be made is that on average, treated patients tend to progress at relatively slow rates, but there is a subset of patients who can progress at fast rates, usually defined as MD rates worse than -1dB/year . As such, determining an individualized rate of progression is especially important in identifying patients at high-risk of vision loss.

Table 1. Mean rates of Visual Field Progression in Treated Patients

Authors/Study Group	Publication Year	Age (years)	Number of patients (n)	Mean Follow-up IOP (mm Hg)	Baseline Mean MD (dB)	Average Follow-up Period (years)	Subtype	Mean Rate of Progression (dB/year)
Smith SD et al	1996	61.8	191	-	-8.7 ± 6.2	7.1	POAG	Stable Group (+0.06) Progressive Group (-1.26)
Schwartz B	2004	59.0 ± 10.0	30	18 ± 2	$18.0 \pm 5.2^{*\wedge}$	6.69 ± 2.27	POAG	-0.384
Ahrlich KG et al	2010	NTG (62.7 ± 12.8) PXG (72.6 ± 9.4)	NTG (139) PXG (154)	NTG (13.3 ± 2.0) PXG (16.5 ± 3.2)	NTG (-6.5 ± 5.4) PXG (-6.7 ± 7.0)	NTG (5.2 ± 2.0) PXG (5.6 ± 1.8)	NTG; PXG	NTG (-0.35) PXG (-0.64)
Chauhan BC et al	2010	59	81	-	-5.21 ± 3.43	11	POAG	Protocol A (-0.21 ± 0.45) Protocol B (-0.22 ± 0.45)
Medeiros FA et al	2010	DH (63 ± 12) No DH (61 ± 13)	348 (510 eyes)	DH (14.1 ± 5.1) No DH (19.7 ± 6.7)	DH (-3.69) No DH (-2.47)	8.2	POAG	DH (-0.38 \wedge) No DH ($-0.88\wedge$)
Canadian Glaucoma Study Group	2010	65.2	216	No EP (16.3) 1 EP (16.1)	-	No EP (6.0) 1 EP (7.2)	POAG	No EP (0.06 ± 0.47) 1 EP (-0.54 ± 1.10)
de Moraes CG et al	2011	64.9 ± 13.0	587 (587 eyes)	15.2 ± 3.1	-7.1 ± 5.1	6.4 ± 1.7	POAG; PXG; PACG; JOAG; NTG; PDG	-0.45 ± 0.7
Leung CKS et al	2011	49.9 ± 14.0	70 (108 eyes)	-	$75.31 \pm 24.53\wedge$	3.2*	POAG	$-1.15\wedge$
de Moraes CG et al	2012	Timolol (65.2 ± 10.8) Brimonidine (63.3 ± 11.1)	127 (253 eyes)	Timolol (13.9 ± 2.3) Brimonidine (14.1 ± 1.9)	-	3.4 ± 1.0	NTG	Timolol (-0.38 ± 0.9) Brimonidine (-0.02 ± 0.7)
de Moraes CG et al	2013	64.1 ± 12.6	841 (841 eyes)	POAG (15.28 ± 2.9) PXG (16.5 ± 2.9) PACG (16.16 ± 2.9) JOAG (14.96 ± 3.7) NTG (13.34 ± 2.3) PDG (14.40 ± 3.5)	-	6.4 ± 1.7	POAG; PXG; PACG; JOAG; NTG; PDG	POAG (-0.46) PXG (-0.55) PACG (-0.36) JOAG (-0.37) NTG (-0.45) PDG (-0.38)
Heijl A et al	2013	71.4	583	18.1	-10.0^*	7.8 ± 1.2	POAG; PXG	-0.80 ± 0.82
Chauhan BC et al	2014	64 ± 13	2324	17.1	-4.01 ± 4.75	7.4 ± 3.0	POAG; NTG	-0.05
Kirwan JF et al	2014	67.3	2208	-	Better eye (-2.0) Worse eye (-3.2)	6.7*	POAG	-0.1*
Aptel et al	2015	65.9 ± 11.3	228 (441 eyes)	Early POAG (15.1 ± 4.2) Moderate POAG (15.0 ± 3.4) Advanced POAG (14.1 ± 2.9) Severe POAG (13.2 ± 3.1)	POAG (-6.11 ± 7.7)	8.4 ± 2.7	POAG	Early POAG (-0.32) Moderate POAG (-0.52) Advanced POAG (-0.54) Severe POAG (-0.45)
Yousefi S et al	2018	POAG (53.4 ± 12.0) PACG (62.7 ± 9.0)	POAG (282; 440 eyes) PACG (49; 79 eyes)	POAG (16.0 ± 2.8) PACG (14.0 ± 3.2)	POAG (-6.4 ± 5.7) PACG (-6.4 ± 7.3)	POAG (7.6) PACG (7.1)	POAG; PACG	POAG ($-0.23 \pm 0.38\wedge\wedge$) PACG ($-0.29 \pm 0.45\wedge\wedge$)
Giammara S et al	2022	53.07*	40	15.83*	-4.06	25.65	POAG; NTG	-0.07

POAG = primary open angle glaucoma; NTG = normal tension glaucoma; OHT = ocular hypertension; PACG = primary angle closure glaucoma; PXG = pseudoexfoliative glaucoma; PDG = pigment dispersion glaucoma; JOAG = juvenile open angle glaucoma; DH = disc hemorrhage; EP = end-point

* = median; \wedge = visual Field Index (VFI); $\wedge\wedge$ = mean total deviation; \wedge^* = mean threshold value

Table 2. Reported Mean Rates of Progression In Untreated Patients

Authors/Study Group	Publication Year	Age (years)	Number of patients (n)	Mean Follow-up IOP (mm Hg)	Baseline Mean MD (dB)	Average Follow-up Period (years)	Subtype	Mean Rate of Progression (dB/year)
CNTGS Group	2001	63.66±9.86	160	-	-5.84±4.21	3.8±2.2	NTG	-0.39±10.06
EMGT Group	2002	Treated (68.2±4.8) Untreated (68.0±5.0)	Treated (129) Untreated (126)	Treated (15.5) Untreated (20.8)	Treated (-5.0±3.7) Untreated (-4.4±3.3)	Treated (5.6±1.7) Untreated (5.8±1.7)	POAG; PXG	Treated (-0.36) Untreated (-0.60)
EMGT Group	2009	68.0±5.1	118	21.2±4.1	-	6	POAG; NTG; PXG	Overall (-1.08) POAG (-1.31) NTG (-0.36) PXG (-3.13)
Garway-Heath DF et al	2017	Placebo (66.3*) Latanoprost (65.7*)	Placebo (178; 264 eyes); Latanoprost (183; 264 eyes)	Placebo (18.7) Latanoprost (16.3)	Placebo (-2.73) Latanoprost (-2.57)	2	POAG	Placebo (-0.29) Latanoprost (+0.03)

POAG = primary open angle glaucoma; NTG = normal tension glaucoma; OHT = ocular hypertension; PACG = primary angle closure glaucoma; PXG = pseudoexfoliative glaucoma; PDG = pigment dispersion glaucoma;

JOAG = juvenile open angle glaucoma; DH = disc hemorrhage; EP = end-point

* = median; ^ = visual Field Index (VFI); ^ ^ = mean total deviation; ^* = mean threshold value

RISK FACTORS OTHER THAN ELEVATED INTRAOCULAR PRESSURE FOR FAST PROGRESSION IN GLAUCOMA

Data from key landmark glaucoma trials have led to a common conclusion: IOP is the main risk factor for progression of visual damage in glaucoma, as well as the only modifiable risk factor that can alter the outcome of the disease.^[2-4] Further longitudinal studies have demonstrated that higher mean IOP,^[27,28] maximum (peak)IOP,^[4] and standard deviation of IOP^[4] are associated with higher rates of glaucoma progression. Elevated IOP is therefore a well-established risk factor for glaucoma progression and current proven treatment options for glaucoma all involve lowering the IOP by means of medication, laser treatment or surgery.

Identification of other risk factors associated with glaucoma progression beyond IOP is important in distinguishing those patients at higher risk of visual impairment and blindness, helping tailor how aggressive clinicians should aim to reduce the IOP in certain patients. However, our ability to identify, a priori, patients who would progress rapidly is relatively poor, and therefore the careful monitoring of visual function during follow-up is paramount, to adjust and tailor treatment appropriately.

In this section, we will review some factors that have been identified as being possibly associated to disease progression. This is not an exhaustive list, which is beyond the scope of this manuscript.

Glaucoma subtype

Numerous studies have suggested that glaucoma subtypes have different rates of visual field progression. The EMGT study found that untreated patients with PXG progressed faster than patients with high tension POAG, who progressed faster than patients with NTG.

⁽⁷⁾ Similarly, De Moraes et al. found that treated PXG had the fastest rate of global visual field change compared to other subtypes, in addition to the highest mean, fluctuation, and peak IOP during follow-up.^[29] The overall impression from these reports is that patients with PXG tend to progress faster than those with POAG (including NTG), but likely most of these differences are attributed to higher IOP in the PXG group. Nevertheless, these studies suggest that patients with PXG should be monitored closely and possibly treated more aggressively to lower IOP and prevent IOP fluctuation. On the other hand, most studies show that patients with NTG tend to have slow rates of progression,^[7,11,21,30] even when left untreated, suggesting that less aggressive or even no initial therapy, coupled with frequent surveillance of visual function and other parameters, could be an adequate strategy for selected patients with NTG.

Disease severity

There are conflicting reports regarding the association between severity of visual field damage at presentation and rate of change. Two multicenter, randomized control trials reported that there was a positive correlation between the severity of visual field damage at baseline and the rate of glaucoma progression.^[31,32] Yet, other studies did not find this correlation.^[33,34] Furthermore, some studies found that visual field damage at presentation was inversely related to rate of progression.^[35-37] Rao et al. showed in a retrospective, clinic-based study including 310 patients (512 eyes) that there was an overall increase in the rate of progression by 0.02% per year, for every dB of worse MD at presentation. Specifically, in early stages of glaucoma, the rate of progression increased as the severity increased; however, in later stages of the disease the rate of progression decreased with increased severity.^[38] Garg et al. showed that having

baseline central visual field damage (defined as affected points within the central 10°) is predictive of faster global MD progression.⁽³⁹⁾ Based on the literature presented, it is generally accepted that baseline visual field damage is associated to faster rates of visual field progression up to a certain stage of the disease, when this relationship might no longer be true, likely due to a ceiling effect observed on visual field testing, as points already severely affected can no longer progress.

Disc hemorrhage

The association of ODH and glaucoma damage has been the subject of numerous publications.^(3,40,41) ODH occur in most types of glaucoma, but appear to be more frequently observed in NTG.⁽³⁾ ODHs are a well-established risk factor for glaucoma progression. Prata et al. reported a mean global progression rate after a disc hemorrhage of -1.11dB/year.⁽⁴²⁾ Other studies have suggested that central visual field loss is accelerated in glaucomatous eyes with a disc hemorrhage.^(43,44) An et al reported that high frequency disc hemorrhages in the same sector of the optic disc have been associated with significantly worse visual field progression compared to those patients with fewer disc hemorrhages,⁽⁴⁵⁾ whereas de Beaufort et al did not find difference in the rate of visual field progression in patients with a single disc hemorrhage versus those with recurrent disc hemorrhages.⁽⁴⁶⁾ In summary, there is good consensus that patients with ODHs are at higher risk of visual field deterioration, however, there is great variability in the rate or absolute number of patients who progress after a single or even multiple recorded episodes of ODHs. The evidence suggests that patients with ODHs should be monitored more closely, and target pressure might be adjusted in these patients.

Myopia

The role of myopia in glaucoma progression is controversial. Many studies proposed that myopia is a risk factor for visual field progression,^(27,47) while others suggested that myopia does not contribute to glaucoma progression, and may, in fact, be a protective factor.^(48,49) The variability in these results may be attributed to the difficulty in discerning visual field defects related to myopia from glaucomatous visual field defects, as well as larger variability of visual field results in highly myopic eyes.

Topical medication compliance

Although clinicians prescribe medication for treatment of glaucoma, patient adherence to topical medication

regimens are known to be poor.⁽⁵⁰⁾ An interesting study utilized visual field and pharmacy data from a large cohort of glaucoma patients to investigate the relationship between topical medication compliance and rate of visual field progression.⁽⁵¹⁾ Among 6,343 patients with a mean follow-up of 5.8 years, the average treatment adherence was found to be 73%. After controlling for confounders and the interaction between time and baseline disease severity, the model indicated that MD progression was significantly reduced by 0.006 dB/year for each 10% increase in adherence.

Age

Several clinical trials and longitudinal studies have identified age as an independent risk factor for progression in glaucoma.^(11,27,52,53) However, when dealing with individual patients, the consensus is not to treat older individuals more aggressively than younger ones but, in fact, to do the opposite. This paradoxical recommendation makes sense when life expectancy is taken into account: for instance, consider two newly diagnosed male patients with moderate visual field defect and IOPs of 24mmHg, one being 50-year-old and the other being 85-year-old. Even though studies would suggest that the older patient has a higher likelihood to progress over the subsequent few years than the younger one, the lifetime risk of visual disability is certainly higher for the younger patient and, therefore, the younger patient should be treated more aggressively to avoid this outcome.

PRACTICAL RECOMMENDATIONS AND TOLERABLE RATES OF VISUAL FIELD PROGRESSION

As glaucoma is a progressive disease, visual field progression may continue to occur despite appropriate treatment. In fact, with longer life expectancy, it is assumed that most patients will eventually progress during their lifetime. In fact, when following patients over long periods of time, the most clinically relevant question is not if progression has occurred, but, rather, if the observed progression rate is likely going to affect patients QoL for the remaining of their life. As such, clinicians must determine the rate of change as soon as possible after initial diagnosis and establish tolerable rates of progression, beyond which more aggressive treatment strategies, such as surgery, should be employed. This tolerable rate of progression should not be the same for every patient, but rather individualized, as it would be influenced by

baseline visual field status, age, general health status, family history of visual disability from glaucoma, among other factors. The goal when determining this tolerable rate of change is to avoid significant visual impairment and blindness for that particular patient and, at the same time, avoid potential risks and side effects from unnecessary aggressive therapy.

In order to establish a baseline rate of progression with reasonable degree of confidence, a sufficient number of visual field tests are required. Chauhan et al. suggested that at least six visual field tests in the first two years are necessary in order to confidently identify 'fast progressors' (rates worse than -2dB/year).⁽⁵⁴⁾ Furthermore, clinicians must use the same test strategy for serial perimetry and exclude tests of poor quality to ensure accurate assessment. Lastly, although visual field testing plays a pivotal role in clinical decision making, it must be coupled with regular clinical examinations with specific attention to IOP, compliance, presence ODH and objective structural assessment with OCT.

Salonikiou et al. developed a model based on data from a cross-sectional, population-based study of an European population to estimate the maximum tolerable rate of progression over an estimated lifetime to avoid visual impairment, defined as a MD of -12dB or worse, and blindness, defined as a MD deviation of -24dB or worse.⁽⁸⁾ Among those with a reliable visual field, 123 patients were included (average age of 73 years and a baseline MD or -3.65dB); 69.1% had a calculated maximum rate of visual progression to avoid visual impairment slower than -1dB per year.

Furthermore, 72.4% had a maximum rate of progression to avoid blindness slower than -2dB per year. This study provides an estimate of an average rate to avoid visual impairment and blindness in a small cohort. We should consider, however, that this estimation is highly dependent on the characteristics of the population: it should be noted, for instance, that the mean age at baseline in this population was 73 years, which is probably higher than the initial age at diagnosis in many patients.

Since glaucoma, once diagnosed, is a lifetime disease, and life expectancy has increased considerably in the last few decades, it is important to clearly understand the long-term outcomes of patients under active care. Giammaria et al. recently published the long-term results of a prospective cohort study of patients with open angle glaucoma actively managed ($n=40$) and healthy controls ($n=29$) monitored with visual field

tests every 6 months for at least 15 years. After a median follow-up of 25.6 years in the glaucoma group and 19.6 years in the control group, the mean rate of MD change was -0.07dB/year in the glaucoma group, and 0.05dB/year in the control group. After adjusting for covariates, the mean sensitivity change was -0.032dB/year faster in the glaucoma group than in the control group, but the differences were not statistically significant. Of interest, 78% of individuals with glaucoma had rates of mean sensitivity change within the range observed in normal controls. This study confirms that in patients with glaucoma who are actively managed with regular visits, progression tend to be slow and not lead to significant visual disability in most cases, even after 25 years of follow-up.⁽⁵²⁾

Some practical recommendations regarding visual field monitoring in glaucoma:

- After diagnosis and initiation of therapy, clinicians should monitor visual fields closely to identify as early as possible the small subset of "fast progressors". These patients might be identified by event-based analysis such as GPA, if progression is detected soon in the first 2 years of follow-up, or by trend-based analysis if you are able to perform enough tests early on to confidently determine a rate of change.
- With longer follow-up, we recommend that clinicians pay greater attention to trend-based analysis, to determine how fast patients are progressing and how likely they are to develop visual disability in the future. If that is the case, therapy might need to be augmented with the goal of achieving lower target pressures and alter the rate of change to prevent visual disability.
- Points close to the center of the visual field flagged on GPA can be very consequential, even if the overall rate of change is not alarming, as seen in Figure 2. Localized losses close to the center of the visual field can be clinically relevant but missed in trend-based analysis of global indices such as VFI or MDI.

This review article attempts to guide clinicians in determining what would be tolerable rates of progression in individual patients, to avoid unnecessarily aggressive treatment for patients who are unlikely to become visually disabled from glaucoma. Tolerable rates of change need to be individualized for each patient and will likely not achieve good agreement among clinicians. Clinicians should make every effort to recognize, as early as possible, patients who are at greater risk of

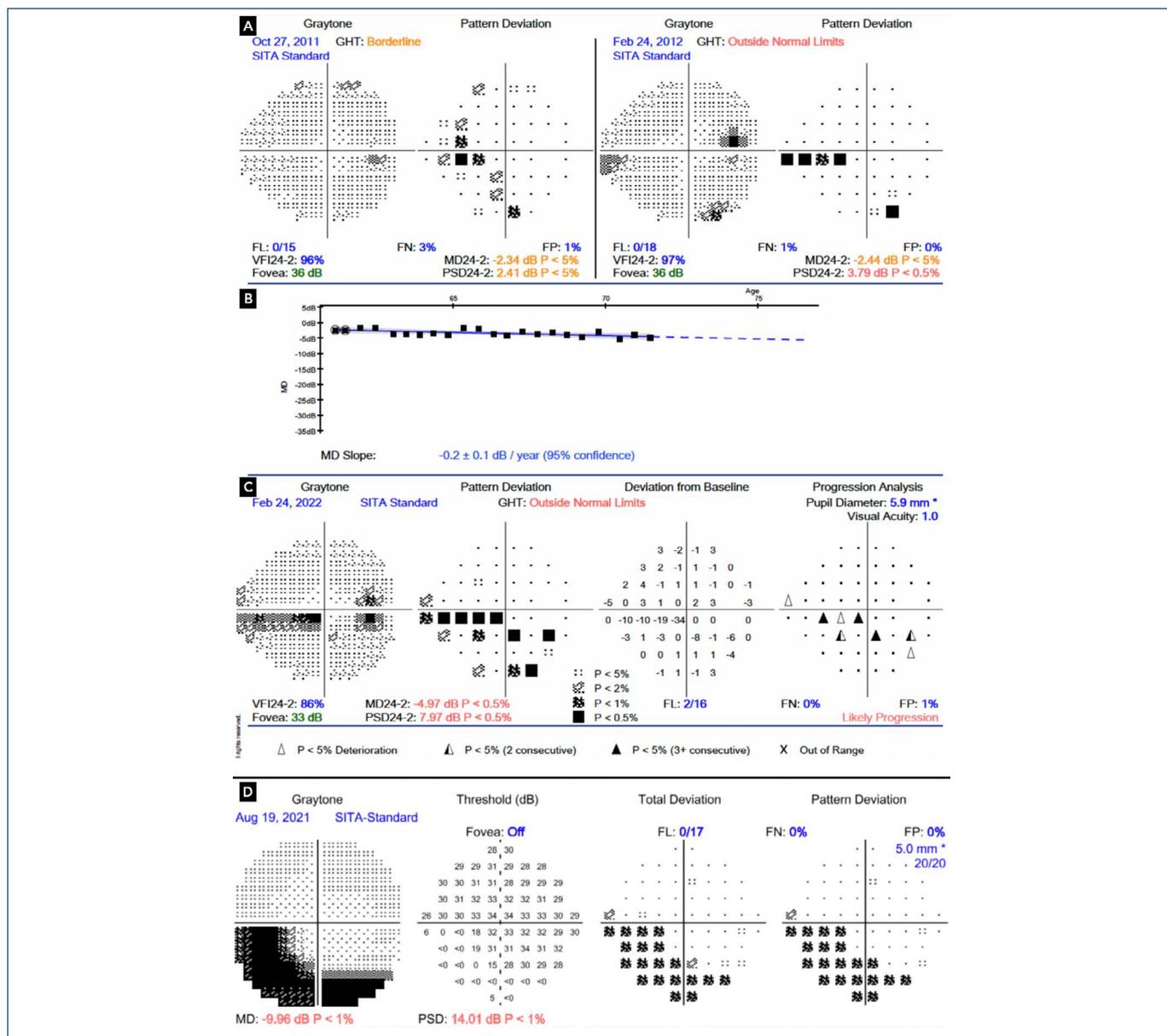


Figure 2. Example of visual field tests from a 71-years old female patient followed for 11.5 years. (A) The two baseline tests (from 2011 and 2012); (B) the graph of the mean deviation rate of change of -0.2 ± 0.1 dB/year; visual field index rate of change was -0.8 ± 0.3 %/year (data not shown); (C) the latest visual field test with glaucoma progression analysis labelled likely progression, highlighting significant change occurring at a paracentral point inferiorly; (D) a 10-2 test confirming the dense defect inferior close to fixation. The interpretation is that despite slow rate of change observed in this patient over 11 years, the progression is occurring predominantly close to the center inferiorly, and it was clearly picked-up by glaucoma progression analysis; the 10-2 test confirms a dense defect inferiorly, and the patient should be managed aggressively.

becoming visually disabled. These high-risk patients would include those already presenting with advanced disease or those progressing at fast rates, usually defined as worse than -1 or -2dB/year. For younger patients already presenting with moderate disease or worse, progression rates much slower than -1dB/year could already exceed what is tolerable. Patients identified with rates of change exceeding what is tolerable should be treated aggressively in order to preserve their visual function and quality of life.

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