Main topic issue No 2:
Glaucoma Concepts – Rate of Progression

Glaucoma Now is a continuing medical education publication. Distributed worldwide to approximately 40,000 ophthalmologists, our goal is to educate and update general ophthalmologists, glaucoma specialists and ophthalmology residents.

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Core Concepts

- Rate of progression is defined as the amount of progression over time, which is used to project the increase of glaucoma damage.
- The goal of treatment is to prevent loss of visual function and ultimately quality of life.
- A progression rate of –2 dB per year is rapid and corresponds to going from a full normal field to perimetric blindness in about 15 years.
- Risk factors that may be associated with progression include older age, greater glaucoma damage, pseudoexfoliation syndrome and disc hemorrhages.
- Perimetrically measured visual function has been adopted by all ophthalmology professionals, but it is the global summation of visual function at all locations, that best helps to understand how patients are doing now and predicts their prognosis.
- From natural history data, patients with pseudoexfoliation syndrome progress most rapidly, followed by high-tension glaucoma patients and ultimately normal tension glaucoma patients.

Rate of Progression Concept

“Rate of progression” can be misunderstood. “Rate” in English means both the speed at which something happens and the frequency of instances (a fraction or a percentage) or number of times that something has happened. Rate of progression has been used both ways in glaucoma, e.g. as the number/percentage/fraction of patients who have progressed (failure rate), and as the speed of progression. 3, 4, 5, 6.

In this text rate of progression will refer to speed of progression. Whereas eyes with higher rates of progression are deteriorating more rapidly, lower rates mean slower worsening.

Thinking of rate of progression as speed of progression rather than risk of progression or observed fraction of progressed eyes/patients is something that has been much more common in recent years. This may be a shift in paradigm. We hoped our treated glaucoma patients would not worsen at all, with every convincing sign of progression seen as a reason to step up treatment. Now, the large trials and other studies (cf Evidence from clinical trials below) have revealed the progressive nature of glaucoma, that most glaucoma patients will suffer some progression if monitored long enough with reasonably sensitive methods.

Assessing and using rate of progression clinically projects the observed change, i.e. increase, of glaucoma damage forward. We aim to see if disease progression during the period of management is safe, or whether the disease is progressing at such a rate that the patient’s visual function and Quality of Life is threatened in their likely life-span. The goal of glaucoma treatment, as formulated by the European Glaucoma Society, is: To prevent loss of visual function and loss of Quality of Life (QoL). Assessing rate of progression is a necessary part of modern individualized glaucoma management.

We do not know how much visual damage is necessary before Quality of Life is jeopardized, but if less than half of the visual field remains in the better eye, most questionnaires will find measurable loss of QoL.

When rate of progression of visual function damage is measured we most commonly follow changes of mean deviation (MD) in decibels (dB) per year. Slow progression rate could be, e.g., 0.2 dB/year – which corresponds to going from a full normal field to perimetric blindness in about 150 years, while a rate of progression of 2 dB/year is rapid progression, corresponding to going from a full normal field to perimetric blindness in about 15 years. MD in dBs is available both in the Humphrey and the Octopus perimeters. The new visual field index (VFI) of the Glaucoma Progression Analysis II (GPA2) program of the Humphrey perimeter instead expresses rate of progression as a percentage of a full field per year.

When measured in perimetric logarithmic units, glaucoma visual field progression is usually linear if observation time is long and the number of observations is large (cf Measurement of field versus disc below). With fewer observations, variation in results often obscures the picture. Theoretically, progression should accelerate—at least over very long time periods—since the risk of progression increases both with older age and with increasing field loss. 5, 9

Importance

Rate of progression is really important for the patient. Over a long—and particularly a life—perspective it is rate of progression that will determine whether the patient can live a normal life with normal or near normal QoL, or whether she/he will suffer from visual disability and loss of QoL. Look at the 2 examples in Fig. 1. Both patients start out with small or limited damage and no subjective problems. Patient (A) with a low rate of progression fares well also over a long time perspective, while the more unfortunate patient with the high rate of progression (B) ends up with serious problems (Fig. 1).

Rate of progression is also really important for the physician. By identifying the large minority of patients, who progress rapidly (often despite ocular pressure (IOP) readings always within the statistically normal range), the physician realizes these patients have great risk of visual impairment; treatment...
can be intensified to prevent too much extra damage. To do this within a few years requires more frequent field testing initially after diagnosis, than has been common in the past. From the large randomized clinical trials, we know every mmHg of extra IOP reduction is associated with a significant reduction of the risk of progression, we have both incentive and duty to identify early those patients with rapid disease progression (cf below).

The most important factors for faster disease progression include higher IOP, older age, more glaucoma damage, pseudoexfoliation syndrome and disc haemorrhages. These factors are useful, e.g. when first setting target pressures after diagnosis. Risk factors have limited value, however, since rate of progression varies so very much even among patients with the same risk factors.

Once we have followed a patient long enough and measured damage enough times, we are able to calculate rate of progression; then we ignore most of the risk factors, and base clinical management on the observed rate of progression. Since progression tends to be linear over time as long as the management (and the IOP levels) are approximately the same, we can improve predictions by using data gathered from the patient, rather than on group data, which is on what the risk factors are based.

By using rate of progression for clinical decision-making during long-term glaucoma follow-up, we replace the guess-work of group risk factors with patient-specific evidence of disease development that the patient’s observed rate of progression represents.

**Measurement of field versus disc**

Glaucoma progression is approximately linear in most cases if measured in the common global MD index. MD is a measure of the mean deviation from the age-corrected normal threshold sensitivity values, which are logarithmic. The linear decay of MD over time seems to be a rule in most patients also if we look over long time perspectives – 10 years or more. If we plot structure-function relationships with perimetric measures like MD on one axis and retinal nerve fiber layer (RNFL) thickness on the other axis in a cross-sectional study involving many glaucomatous eyes, we find typically a curvilinear relationship with little change in MD in early stages of structural change and small changes in structure in moderate or severe disease.

If we were to measure progression with a non-logarithmic unit, e.g. RNFL thickness, it is most likely that rate-of-progression would not be linear over long time periods (but probably over short period of 2–4 years). This and the fact that we are trying to prevent disease progression to a severe functional stage are good reasons not to use disc or RNFL measures to define rate of progression. In the future we might get tables translating structural measurements to functional units, and we could then base rate of progression measures on structural measures, after translation of the structural findings to functional units. Probably at least in moderate or severe stages of the disease these translations from structure will not work well, since rather large changes of changes in MD or VFI will correspond to very small structural changes. The rate of progression expressed in structural/anatomic measures might be interesting, but difficult to use in management. A statistically significant worsening of a structural parameter probably means the patient is deteriorating, but is uncertain clinically, since we cannot translate the structural measurements to the visual function domain. Clinical management requires the present visual field and the rate of progression of visual field defects (Fig. 2).

Improvement of glaucoma care needs perimetrically measured visual function. Progression rates will vary greatly among test point locations; blind points will not progress, and also many normal points will be stable, while a subset of test point locations often surrounding existing deep field defects will show rapid progression. Global summation of the visual function at all locations indicates the overall trend that best helps us to understand how the patient is doing and how the patients visual function will develop in the future.

**Fig. 2 Judging the clinical relevance of progression is much easier with access to field data. If we cover the fields on the right side of the picture, the disk photographs show us that the eye has very clear glaucoma, and that it is progressing over time. But if we look at the field series we immediately also recognize that progression is large a threatening and that the eye has advanced visual field loss.**
Evidence from clinical trials

We now have information of the natural history of visual field progression in glaucoma. The Collaborative Normal Tension Glaucoma Study (CNTGS) reported a low mean rate of progression of 0.43 dB/year in patients with normal tension glaucoma. Recently, natural history progression rates were reported from the Early Manifest Glaucoma Trial. Patients with normal tension glaucoma were included in EMGT, and the mean rate of progression was similar in EMGT (0.36 dB/year) to that in CNTGS, thus confirming the results from the latter study. Just as in CNTGS inter-patient rate of progression variability was very large in EMGT, also among patients with similar IOP levels.

EMGT results further showed that the mean rate of progression in POAG with elevated pressures was considerably and significantly higher than in NTG, at 1.31 dB/year, while on the average eyes with exfoliation glaucoma progressed very rapidly at more than 3 dB/year corresponding to going from a normal field to perimetric blindness in less than 10 years (Fig. 3). These rates are similar to those calculated from cross-sectional data.

While other large randomized trials have not published as detailed results on rate of progression, progression was frequent and early in several of them. In Advanced Glaucoma Intervention Study (AGIS) the mean field loss after 7 years was 1.6 AGUS units, which corresponds to about 2.3 dB i.e. over 0.3 dB/year. Progression rates depended very much on IOP levels during follow-up.

In a large retrospective study of clinically managed glaucoma patients, mean rates of progression were smaller but of similar magnitude to those of the natural history studies; inter-patient variability was huge.

However, there is a lack of data on typically encountered rates of progression in clinical care and from prospective studies. We need a better understanding of patients’ performance as a benchmark for clinical glaucoma care, and to assess the met and un-met needs of glaucoma patients.

REFERENCES

1) Introduction

Glaucoma is a multifactorial neurodegenerative disorder characterized by progressive structural and functional injury of the optic nerve complex (optic nerve + parapapillary region) for which intraocular pressure (IOP) remains the only proven modifiable risk factor. Assessments of both structure and function of the optic nerve are indispensable aspects of the glaucoma examination and disease detection, monitoring, and management. [1] Since the main goal of treatment is to either halt or slow disease progression, clinicians must be able to indentify patients at increased risk of progression and, most importantly, be able to detect and measure progression when it occurs.

Glaucomatous progression can be detected clinically either by structural or functional tests, with change detected by either event-based or trend-based analysis.

2) New Technologies/ Software

A. Functional Tests

Standard automated perimetry (SAP) is the most widely used method to assess visual function in glaucoma and correlates well with patient quality of life and vision. SAP has also been used in the major randomized clinical trials (RCT) to determine glaucoma functional change or progression endpoints.

Different types of event-based VF progression criteria were used by each of these trials. However, a widely used statistical package of event-based analysis is automatically provided by the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Inc., Dublin, CA) and is called Guided Progression Analysis™ (GPA) (Carl Zeiss Meditec, Inc., Dublin, CA). The Humphrey Field Analyzer II-i with the new GPA software additionally provides a trend-based analysis using the Visual Field Index™ (VFI) (Carl Zeiss Meditec, Inc., Dublin, CA) described by Bengtsson and Heijl, along with the more familiar event-based analysis.[2]

The VFI is an age-adjusted index that summarizes the global VF status for each test of the VF series. Briefly, the VFI calculation is based on the pattern standard deviation (PSD) probability maps with a greater weighting for more central points. Therefore, the final index which ranges from 0 (blind) to 100% (normal) has a greater weight of the central points relative to the paracentral and peripheral points. (Figure 1). A minimum of five exams over at least three years must be included in GPA 2 for the linear regression results to be presented.

Fitzke et al. described a graphical method of measuring rates of VF change using pointwise linear regression (PLR) analysis which was further employed to build the Progressor™ software package.[3] At least five tests are necessary for the analysis to provide the global rates of change (dB/yr) and p values. The software also allows one to define different progression criteria (Figure 2 B). If any of the tested points meets the chosen criteria a graphical display shows the lo-
cation of the progressing point (s) on the VF, as well as the level of significance of the slope (p) (Figure 2 C and D).

For those who use the Octopus Perimeter (Haag Streit, Berne, Switzerland), the PeriTrend™ provides a trend-analysis; this is part of the device’s standard statistical package. Similar to GPA 2, this is a form of trend-analysis based on global indices and therefore has the limitation of not detecting focal change.

**B. Structural tests**

**Stereo disc photographs**

Review of simultaneous or non-simultaneous stereophotographs of the optic disc and retinal nerve fiber layer (RNFL) remains the most widely used method to detect structural change in glaucoma. Masked photograph review was used by some of the major RCTs to determine structural progression.[4-6]

**HRT**

New imaging technologies have been developed to evaluate objectively the optic disc and retinal nerve fiber layer and to enhance identification of structural progression. (Figure 3). Confocal Scanning Laser Ophthalmoscopy (Heidelberg Retina Tomograph, [HRT], Heidelberg Engineering, GmbH, Heidelberg, Germany) was among the first devices designed to do this. The Topographic Change Analysis™ (TCA) program was developed to allow objective measurements of topographic change in a series of HRT examinations. Due to its stable platform, data from the older version of HRT (HRT II) can also be analyzed using the current version of the software (HRT III). (Figure 4). TCA currently also provides objective, trend-based measurements of rates of changes (mm2/yr). Moreover, a regression line is provided both globally as well as for each stereometric parameter on the printout. Recent reports have applied linear regression to HRT longitudinal data suggesting that this method may be useful to quantify rates of progression using the HRT. [7,8]

**GDX**

Scanning Laser Polarimetry (GDx-VCC and GDx-ECC, Carl Zeiss Meditec, Inc., Dublin, CA, USA) is an additional technology used to detect structural progression. The new Guided Progression Analysis™ (GPA) software provides both an event- and trend-based analysis of longitudinal change of the RNFL thickness. A colored map with a classification system resembling the HFA GPA is also provided: yellow, possible progression; red, likely progression; and purple, possible increase (RNFL “thickening”). Graphical images of the linear regression (microns/yr) of values for the average RNFL thickness as well as for the various RNFL sectors are also shown along with its extrapolation over time, assuming the rate remains constant (Figure 5). There is a good correlation between RNFL thickness change shown on Gdx and conventional progression endpoints (SAP and photograph review).[9]

**OCT**

Time-domain optical coherence tomography (Stratus OCT, Carl Zeiss Meditec, Inc., Dublin, CA, USA) has also been reported to be able to assess structural progression. The new version of the software, the GPA Advanced Serial Analysis, provides the rates of RNFL thickness change (microns/yr) and their level of significance (p) both globally and by clock-hours (Figure 6). This feature may
allow topographic correlations between localized RNFL loss and VF progression. Detection of structural progression using time-domain OCT has been demonstrated using both topographic and RNFL parameters of the device. [10]

Improvements in the OCT technology (Fourier-domain OCT) are available and due to their rapid image acquisition with high-resolution, may improve performance of the devices from several companies, to detect structural change.

in a subset of the Advanced Glaucoma Intervention Study (AGIS) population and found results consistent with the previously documented importance of risk factors for progression (e.g., intraocular pressure [IOP] and age).[11] In the Diagnostic Innovations in Glaucoma Study (DIGS), rates of structural loss using different technologies can be measured in glaucoma patients and suspects; these values correlate well with the follow-up IOP and SAP/optic disc endpoints. [9,10] Large studies involving real-world patients have shown that trend-analysis may be an effective method to determine progression with results consistent with the major clinical trials.

4) Conclusion

These functional and structural methods to determine rates of progression ought to be tested in populations enrolled in the major clinical trials in order to assess their performance and consistency with previously reported risk factors. New, more accurate, and improved software algorithms should continue to be developed to allow clinicians to detect better structural and functional changes in glaucoma so that treatment paradigms can be modified to prevent visual disability.

References


Glaucoma is a chronic optic neuropathy in which progressive neurodegenerative loss of retinal ganglion cells results in increasing damage to the visual field, potentially leading to blindness. From the natural history of glaucoma, progression is very common without treatment: more than 60% of untreated patients in the Early Manifest Glaucoma Trial (EMGT) experienced progression of visual field damage in 5 years.

Even though progression to blindness is relatively rare, a cohort study following glaucoma patients for more than 20 years found that, despite treatment, almost 20% of patients went blind. Results from the same study highlighted the wide variation in damaging intraocular pressure (IOP) levels between individuals; some patients went blind at IOP values that other patients could tolerate without progression.

This introduces the concept of Target Pressure: the IOP (or range of IOP values) that the treating ophthalmologist aims to achieve to try to preserve optic nerve head health. It depends on the level of untreated IOP, the patient’s age and life expectancy, the level of glaucoma damage and the progression rate.

Visual Field values need to be monitored carefully and treatment should be adjusted if speed of progression threatens visual disability.

Even a small (1 mmHg) reduction in IOP could reduce significantly (around 10%) glaucoma progression.

Monotherapy is indicated as an initial treatment approach, which may then lead to combination treatment or non medical therapies.

The concept of target IOP is not evidence-based although data coming from the large National Institute of Health trials helps us with a starting point. For rates vary between different patients, target IOP also vary. As stated in the European Glaucoma Society Guidelines, target IOP depends on the level of untreated IOP at baseline, the patient’s age and life expectancy, the level of glaucoma damage and the progression rate of that damage (Figure 1). There is no magic number that will be safe in all patients, but the choice of the target IOP should be individualized and the accuracy of our choice should be verified by checking visual function during follow-up.

Assessment of the rate of progression is particularly important to verify the choice of target IOP: if the new slope (after target IOP is reached) of the line of MD changes (or Visual Field Index (VFI)) improves over time so that visual function will not be affected significantly during the patient’s lifetime, then the target IOP has been chosen correctly. However, if the new rate of progression is still risky for the patient, a lower target IOP should be selected.

The concept of target IOP is not evidence-based although data coming from the large National Institute of Health trials helps us with a starting point. For
relatively early glaucomas (cf. Collaborative Initial Glaucoma Treatment Study (CITGS)) an IOP reduction of about 35% will control the disease in the vast majority of cases, while for more advanced disease (cf Advanced Glaucoma Intervention Study (AGIS)) an IOP constantly below 18 mmHg would be a reasonable target (Figure 2). From these trials (e.g. Ocular Hypertensive Treatment Study (OHTS), EMGT), is even a small amount (1 mmHg) of reduction in IOP could reduce (around 10%) glaucoma progression significantly. Every single mmHg counts and, for progressing patients it might make a difference.

Development of a therapeutic strategy must keep this in mind. Monotherapy is always preferable initially to reach the target. However, as reported in the CIGTS, the majority of glaucoma patients (75%) need more than one drug to reach target IOP.

Remember to judge the adequacy of the target IOP according to the effect on visual function (rate of progression). If medical therapy alone is not enough, then other options (e.g. laser and/or surgery) should be considered without delay.

References:
Practical Tips:
Frequency of Visual Field and Disc Imaging

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Core concepts
- Several indices can be used for measuring rates of visual field progression: Mean Sensitivity (MS), Mean Deviation (MD) and the Visual Field Index (VFI).
- Clinicians are most familiar with measuring MD.
- More examinations are required with a lower MD progression rate and a higher MD variability.
- A relatively slow change of 0.5 dB/year over only 2 years will require 7 examinations per year to detect progression.
- To identify rapidly progressing patients (MD rates of -2 dB/year or worse), 6 examinations in the first 2 years of follow-up are recommended.
- Clinical decisions based on visual field progression require more than a formulaic approach; aspects of the visual field as well as the overall clinical picture need to be taken into account.

Visual field assessment remains the cornerstone of glaucoma practice; it provides key diagnostic information on the progression of the disease. Knowing the visual field, and whether and how much it is changing helps the clinician to optimize management and follow-up of the individual patient with the aim of achieving the best functional outcomes.

Together with age and stage (or severity) of visual field loss at diagnosis, the rate of visual field change is vital to gauge the likelihood of visual disability (Fig. 1). Rate estimates usually cannot be made with few examinations and generally, the frequency of visual field examinations falls below recommended levels.1

Several indices can be used for measuring rates of visual field progression: global indices such as Mean Sensitivity (MS), Deviation (MD) or the Visual Field Index (VFI),2 and visual field sectors or individual point-wise values.

**FIGURE LEGENDS**

Fig. 1: A. Young patient (55 yrs) with early visual field loss and a rapid rate of progression (-2 dB/yr) can be expected to have visual disability by age 70 years, but with a slower progression rate (-0.2 dB/yr), he or she may not experience lifetime visual disability.

B. Older patient (70 yrs) with moderately advanced loss and a rapid rate of progression can be expected to have visual disability by age 80 years. With a long life expectancy and a slower rate (-0.2 dB/yr), the patient may experience borderline visual disability.
While the VFI corrects the degree of visual field loss for a diffuse reduction in sensitivity and therefore is less sensitive to effects of cataract, to date, clinicians are most familiar with MD. Sectoral and point-wise analyses can be very helpful, but this article will discuss only MD.

Rates of visual field change in glaucoma vary considerably. The ability to detect statistical change depends on (i) the rate (the amount of MD change over time); and (ii) the variability of MD measurements. Generally, to detect a rate of change, the number of examinations required increases with a decreasing MD rate and higher MD variability: to detect a slowly progressing visual field with highly variable examinations requires more examinations while to detect a faster progressing visual field with less variable examinations requires fewer examinations.

A recent publication provided the number of examinations required to detect various rates of visual field change with different levels of visual field variability. Table 1 summarizes this key information assuming moderate visual field variability and illustrates the frequency of examinations required to detect various rates of change over 2, 3 and 5 years. To detect a relatively slow rate of change (-0.50 dB/yr) over only 2 years requires 7 examinations per year; over 5 years, this decreases to 3 examinations per year. To identify rapidly progressing patients (those with MD rates of -2 dB/yr or worse), 6 examinations in the first two years of follow-up are recommended.

This approach also helps clinicians to decide on the frequency of examinations required to detect a rate of visual field loss that could potentially lead to visual disability, for example after an intervention to reduce the rate of progression.

Finally, clinical decisions based on visual field progression require more than a formulaic approach as any summary index, such as MD, is not sensitive to the topography of visual field defects. Hence MD derived from a small paracentral visual field defect close to fixation merits very different consideration to the same MD derived from a more peripheral visual field defect. Therefore recommended frequencies of visual field examinations are only a guide to be considered together along with aspects of the visual field in the context of the overall clinical picture.

### Table 1. The frequency of visual field examinations required over 2, 3 and 5 years to detect various progression rates.*

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<thead>
<tr>
<th>Progression rate</th>
<th>Number of examinations/year</th>
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<tr>
<td></td>
<td>2 years</td>
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<tr>
<td>-0.5 dB/yr</td>
<td>7</td>
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<tr>
<td>-1.0 dB/yr</td>
<td>5</td>
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<tr>
<td>-2.0 dB/yr</td>
<td>3</td>
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*assuming moderate visual field variability

**REFERENCES**
CME credits can be obtained via the questions on the website very soon.
The process of obtaining CME accreditation for the journal is currently ongoing.

STATEMENT OF NEED AND PROGRAM DESCRIPTION
Recent months and years have seen significant advances in our understanding of glaucoma. Much has been learned, not only about damage mechanisms and pathogenesis, but also about diagnosis and management. Treatment options – both medical and surgical – continue to expand. This program will review this new knowledge with an emphasis on incorporating recent insights into day-to-day practice.

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