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 – 2dB 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 eye care 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.

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 for 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.

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. 1 Examples of two eyes, one with a very slow rate of progression (≈0.1 dB/year) (A), and one with a rapid and dangerous rate of progression (≈2 dB/year).

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.21 Recently, natural history progression rates were reported from the Early Manifest Glaucoma Trial.22 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, were 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 3dB/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.23

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 AGIS 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.24

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.25

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


Fig.3 Natural history of glaucomatous visual field damage. Untreated rates of progression for POAG with high baseline IOP - HTG(≥21 mmHg), with low baseline IOP (NTG) and with pseudoexfoliation glaucoma (PEXG). The total inter-patient range of progression rates (between the red and green dotted lines) is huge. Data from(Heijl et al. 2009).