THE CHALLENGES OF MONITORING GLAUCOMA PROGRESSION

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ABSTRACT

Diagnosing glaucoma progression is complex: it requires the precise assessment of functional loss and structural change compared with baseline measurements. Establishing reliable baseline data is essential in this process. Determining a functional baseline requires repeated visual field testing, while documentation of the optic disc appearance is needed for the acquisition of a structural baseline. The latter can be achieved using both clinical and imaging methods, which are complementary. Although imaging-based modalities to assess absolute and rate of progression are likely to prove more important in the future, more guidance is currently required for their use in clinical practice.

Because the rate of progression provides important information about the risk of vision loss, guidelines recommend determining the rate of progression for each individual patient when planning management. Adherence issues must be addressed before changing the treatment strategy, since poor compliance can play a considerable role in many patients' disease progression.

In conclusion, we must strive to improve the management of glaucoma to limit the impact disease progression has on the patient's quality of life.

KEY WORDS

GDx-Glaucoma Progression-HRT-OCT-Stereo photography-Visual Field.

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INTRODUCTION

Glaucoma is a chronic, progressive optic neuropathy most commonly associated with elevated intraocular pressure (1). Without adequate management, glaucoma can lead to irreversible visual loss and reduced quality of life (QoL) (1). Glaucoma affects approximately 67 million people worldwide and is the second leading cause of blindness in the world (2). Detection of glaucoma progression is crucial for the identification of patients at risk for visual loss (3).

DELAYING PROGRESSION POSES SEVERAL CHALLENGES

Delaying progression assumes first detection of progression, then determination of the rate of progression and finally adjustment of treatment. Treatment decisions should be based on the available scientific evidence and they should be tailored to the individual patient. The goal of glaucoma treatment is to maintain the patient's visual function and related quality of life at a sustainable cost in terms of side effects, financial implications and inconvenience for the patient (3).

DETECTION OF PROGRESSION

Definitions

European and American guidelines describe progression as a worsening of structural and/or functional defects (3,4). More detailed definitions of progression however have not yet been established. Because progression can occur at normal intra-ocular pressure (IOP) levels, reliance on tonometry alone is not possible.

It is essential to assess both structure and function in order to detect progression. Previously, it was generally accepted that optic disc changes precede VF damage. However, the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS) have shown that structural and functional damage seldom coincide in patients converting from ocular hypertension (OHT) to glaucoma, and that visual field changes may precede optic disc damage. The same was shown in glaucoma patients with progression (8-10). Optic disc imaging and visual field measurements are complementary methods to monitor change, and it is likely that visual fields are not the ideal gold standard for the validation of imaging devices.

Statistically significant structure-function correlations exist only in patients with advanced glaucoma (11). Regarding the definitions of structural defects, the European Glaucoma Society (EGS) guidelines describe clinical optic disc assessment (3). However, the clinical analysis remains subjective. Ideally, analysis of structural defects would be both qualitatively and quantitatively objectifiable.

In the evaluation of functional defects, the EGS has made recommendations regarding the frequency of VF testing using specific analysis tools (3). The frequency of testing is to be adapted to the severity of glaucoma damage and the rate of progression (3). This will be discussed further in this article in the section on determination of the rate of progression.

Clinical trials have used varying criteria for glaucoma progression

In the Collaborative Initial Glaucoma Treatment Study (CIGTS), VF scores were generated on the basis of a weighted summary of the deficits on the total probability plot (12). Increasing scores reflected increasing VF loss and ranged from 0 to 20. This differs from the Advanced Glaucoma Intervention Study (AGIS) (13). In the latter, VF defects were scored on a scale from 1 to 20 using a total deviation plot in 3 consecutive VFs. Structural optic disc change was not assessed in either study.

The Early Manifest Glaucoma Trial (EMGT) defined perimetric progression as the same 3 or more test locations showing significant deterioration from baseline in the glaucoma change probability maps from 3 consecutive visual fields (14). Optic disc changes were detected by flicker chronoscopy and confirmed by side-by-side photographs.

In the Collaborative Normal Tension Glaucoma (CNTG) study, the definition of VF change was based on the comparison of threshold values

with baseline (15). Structural change was analyzed by masked assessment of stereo photographs.

Different tests detect progression in different patients

Documentation of both optic disc and retinal nerve fiber layer (RNFL) is possible with the Stratus Optical Coherence Tomography (OCT) and the Heidelberg Retina Tomography (HRT). The Glaucoma Detection System with Variable Corneal Compensation (GDx VCC) analyzes the RNFL. Pupil dilation is necessary for the time domain OCT.

HRT of the optic disc

Confocal scanning laser ophthalmoscopy with the HRT has the longest track record to detect and monitor structural glaucoma progression. Since its release 15 years ago, the operational hard- and software have continuously been modulated while remaining compatible with the old data (16). The stereometric parameters (except for the cup shape measurement) depend on the reference plane and the contour line. To reliably use the stereometric parameters in the assessment of progression, the reference height should probably not differ more than 10% from baseline (17). Topographical change analysis (TCA) is independent of the contour line and reference plane and is likely more reliable to assess structural progression with the HRT.
Kourkoutas *et al.* tried to identify the discrepancies between HRT-defined progression with TCA and progression detected by expert-assessed sequential disc stereo photographs in a report with 54 patients (18). A smaller proportion of eyes met the definition of progression when evaluated using stereo photograph assessment alone (6%, or 3 eyes) compared to isolated HRT-defined progression (30%, or 16 eyes). Detecting progression based exclusively on stereo photographs usually indicated an event such as a disc haemorrhage, blood vessel deviation or rim narrowing. Isolated HRT-defined progression was probably based on surface height change, which is more difficult to assess on photography. These findings confirm that HRT and stereo photographs are complementary in the follow-up of a glaucoma patient.

GDx VCC of RNFL

A study by Medeiros *et al.* evaluated the ability of scanning laser polarimetry to detect progressive RNFL loss in glaucoma patients and patients suspected of having the disease (9). A total of 335 eyes from 195 patients were included, with a mean follow-up of 4 years. GDx VCC scanning laser polarimetry, optic disc stereo-photography and standard automated perimetry (SAP) were performed annually. Progression was determined by masked assessment of optic disc photographs and by glaucoma progression analysis (GPA) of SAP.
Over time, 10% showed progression by stereo photographs and/or SAP. Of those patients, 38% showed progression on optic disc photographs, 41% on VF and only 21% on both parameters. These results confirm that structure and function do not always correlate. Average RNFL measurements decreased significantly over time for both progressors and non-progressors. However, the rate of decline was significantly higher in the progressing group compared to the non-progressing group ($p = 0.001$).

OCT of RNFL

Leung *et al*. assessed structure (RNFL) by OCT. This study included 72 eyes from 41 patients who were followed up for more than 3 years. Stratus OCT and SAP examinations were performed annually. Progression was determined by GPA for average RNFL thickness and by linear regression between mean deviation of SAP and age. 16 eyes showed progression on OCT and 9 on SAP. Only 7 eyes showed progression on both OCT and SAP. The authors concluded that there was a poor agreement between progression by OCT (RNFL) and SAP. These results strongly emphasize the importance of assessing both structure and function in the detection of glaucoma progression.

Technical challenges in the detection of progression

Establishment of a baseline

Establishing a reliable baseline is essential for detection of glaucoma progression. Functional assessment requires repeated VF tests to overcome the patient's learning curve. The first

documentation of a VF defect should be confirmed as soon as possible on at least 2 additional consecutive exams. A series of reliable VF's with more than minor fluctuation in mean deviation suggest progression. However, the VF in stable severe glaucoma shows more fluctuation compared to stable mild glaucoma (20).
Structural assessment requires documentation of optic disc appearance. Colour photographs are almost identical to the image observed during clinical examination, but with two additional advantages: they are magnified and they can later be compared with previous images. Stereoscopic photography (ideally simultaneous, with a fixed angle) is the preferred method of qualitative imaging. Images obtained with digital scanning devices are dependent on software for interpretation. Often, three images are necessary during the first 18 months to distinguish progression from fluctuation. If colour photography is not available, manual drawings are still useful to provide a record of the optic disc appearance.

Challenges in identification of changes in optic disc and RNFL

As mentioned above, optic disc photographs are the gold standard for the structural assessment, but changes can be difficult and time consuming to identify (3). Furthermore, there is a large inter-observer variability and the quantification of changes remains a difficult task. Quantitative imaging can assist the clinician in monitoring progression. In the future, digitized quantitative imaging is likely to prove important in the assessment of progression and rate of progression.
The relationship between VF and HRT change was investigated by Artes *et al*. in a prospective longitudinal study with 84 patients and 41 healthy controls (21). At intervals of 6 months, all participants underwent SAP, high-pass resolution perimetry (single-reversal staircase technique), and HRT examination. During follow-up, glaucomatous change manifested either predominantly in the visual field or predominantly in the optic disc. Few patients showed disc and VF change in the same amount.
However, Strouthidis *et al.* reported on the relationship between a functional map based on interpoint correlations of the VF (HFA) and an anatomical map based on the distribution of the RNFL in the optic disc (22). They concluded there is an association between the strength of correlation between test locations in the VF and the relative location of these points in corresponding RNFL bundles at the optic disc. These findings confirm that both imaging and perimetry are required if progression is not to be missed in patients with OHT or early glaucoma.
It is not yet clear how best to use these available imaging devices. Unambiguous answers to questions regarding which machine best to use, the frequency of testing and the interpretation of data cannot yet be offered. However, HRT is currently the tool with the longest retro-compatibility. It is also important to remember that the developing imaging techniques are still objective adjuncts and that they are unlikely to ever replace a meticulous clinical examination entirely.

DETERMINATION OF RATE OF PROGRESSION

Rate of progression provides important information about the risk of vision loss

Not all patients progress at the same rate. Therefore guidelines recommend determining rate of progression for the individual patient when planning management. It is clear that patient B in figure 1 (3) will never reach severe functional impairment during his/her life. As a consequence, aggressive therapy for patient B is redundant. This is in contrast to patient E who needs an aggressive management to maintain an acceptable QoL.

Regular visual field assessment is recommended to identify the rate of progression

Evidence-based guidance on the frequency of visual field examinations required to identify clinically meaningful rates of change in glaucoma have only recently become available (23). Tables a and b illustrate that three examinations per year are required to identify an overall change in mean deviation (MD) of 4 dB over 2 years in a patient with average visual field

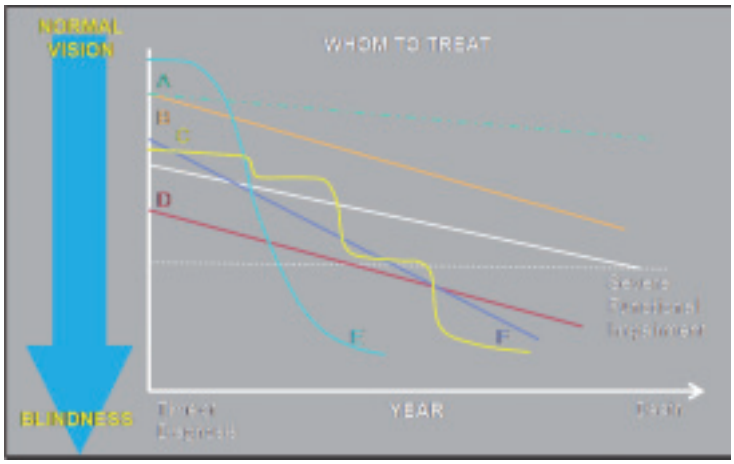

Fig. 1: Evaluation of whom to treat (3).

variability (23). From these results one can deduct the recommendation to perform 3 VF's (SAP) per year in the first 2 years of follow-up. The rate of VF progression can subsequently be assessed. Afterwards 1 VF per year, with control if change, is sufficient. "There are many circumstances when the frequency of examinations should be increased because of a higher perceived risk of functional loss, for example, suspicion of optic disc change, inadequate IOP control, advanced field damage, pseudo exfoliation, increased age and morbidity in the fellow eye" (23). We would like to emphasize that non-conventional perimetry (e.g. Frequency Doubling Technology and Short Wavelength Automated Perimetry) can support but not replace SAP.

Table a and b: *Rates of visual field change corresponding to total change in MD over 2, 3 and 5 years (a) and the number of visual fields per year required to detect the corresponding change with 80% power (b) (3).*

	Progression rate (dB year)		
(a) Total MD change (db)	2 years	3 years	5 years
-1.0	-0.5	-0.3	-0.2
-2.0	-1.0	-0.7	-0.4
-4.0	-2.0	-1.3	-0.8

	Annual examinations		
(b) Total MD change (db)	2 years	3 years	5 years
-1.0	7	6	4
-2.0	5	4	3
-4.0	3	3	2

INTEGRATION OF VISUAL FIELDS INTO CLINICAL PRACTICE

It is important to use the same strategy (threshold algorithm) for repeat VF examinations (3). Both Humphrey and Octopus automatic perimetry can be performed in the standard or in shorter screening modes. The classic "staircase" bracketing strategy has been replaced by faster algorithms. The standard strategy for Humphrey automatic perimetry (HFA) is SITA Standard (±6-minute testing time). SITA fast is a shorter strategy (±3-minute testing time) that can be used for screening and follow-up, but it is slightly more difficult for the patient. The standard strategy for the Octopus is the Dynamic Strategy (±6-minute testing time). Fewer test locations in less than 4 stages (e.g. 32 test locations in 2 stages) can be used for screening (±3-minute testing time). However, 4 stages (59 test locations) are more appropriate when following up VF damage. Tendency-oriented perimetry (TOP) is another fast algorithm from Octopus that can be used for screening purposes.

In glaucoma, the VF is performed in the central 24° field. This area correlates with the distribution of the majority of retinal ganglion cells and corresponds to the 24-2 program for HFA and the G1/G2 program for the Octopus. Compared to the 30° programs (30-2 for HFA or 32 for Octopus), there is only a small reduction in information, but with the advantage of having fewer artefacts.
Computer-assisted progression determination exists in 2 modes: it can be event- or trend-based (3). The event-based mode is designed to determine whether the VF has progressed compared to baseline (e.g. Glaucoma Change Probability maps, GPA (figure 2). These programs require a minimum of 5 tests to exhibit likely progression (3). In contrast, the trend-based computer-assisted mode is designed to determine rates of progression (figure 3) (e.g.

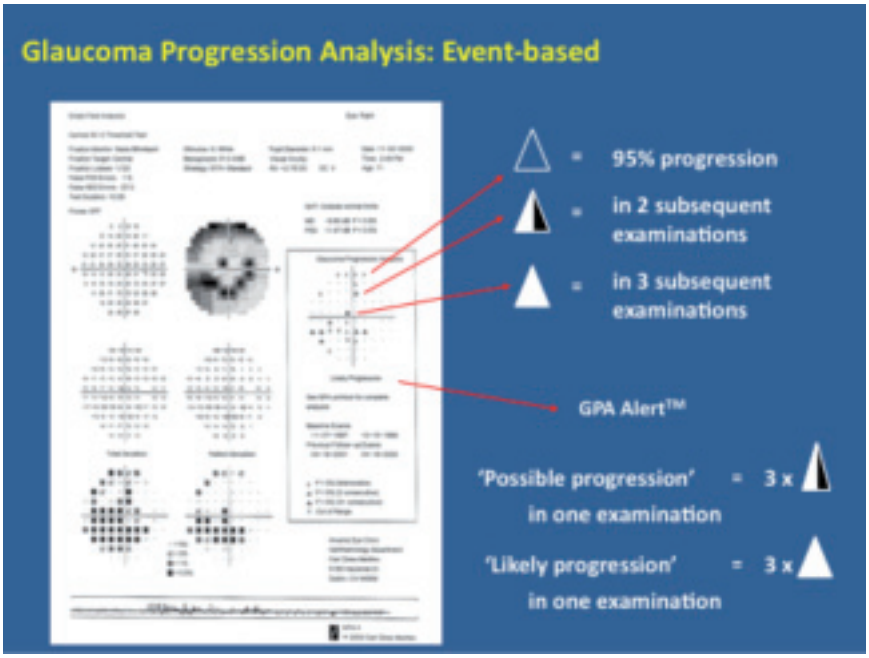

Fig. 2: Example of event-based analysis of test locations using GPA: compares baseline and last follow-up examination.

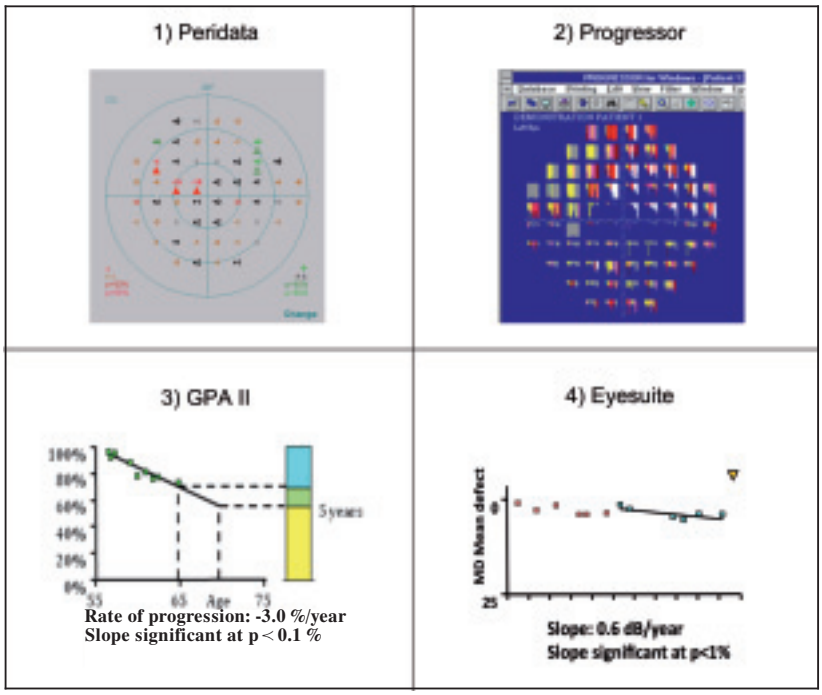

Fig. 3: Examples of software programs calculating rates of progression.
Peridata (1) and Progressor (2) are both compatible with Humphrey, Octopus, and several other machines for point-wise and index regression analysis. Guided Progression Analysis (GPA II) (3) (compatible with Humphrey) and EyeSuite (4) (compatible with Octopus) perform regression analysis of the indices.

Peridata and Progressor for point-wise and index linear regression analysis, or EyeSuite and GPA II for linear regression analysis of the indices) (24-28). The correlation between event- and trend-based progression analyses is moderate. To quote Artes and Chauhan (21) "…while event-based analyses may have merit when there are a limited number of observations, with longer follow-up and frequency of examinations the rate of change or its statistical significance may provide more clinically useful information." Both types of analyses can be complementary, but only trend-based analysis will determine the rates of progression.

PROGRESSION AND ADHERENCE

Following the detection of progression, subsequent management decisions are crucial. These can consist in the modification of therapy and/or the establishment of a new target IOP. Patient management should be based on risk factors such as baseline damage, age, and IOP (23).

Before changing treatment strategy, adherence issues need to be addressed. The investigation of Vandenbroeck S *et al.* on non-adherence of glaucoma patients concluded that poor compliance correlates with lack of patient understanding of their condition, younger age, male gender, higher frequency of dosing and low frequency of follow-up visits (29,30). Forty percent of glaucoma patients admit to missing one or more doses during the previous 2 weeks: 12% admit to missing two or more doses during the same period. Moreover, ophthalmologists tend to overestimate patient adherence. Systematic assessment of non-adherence and its risk factors are essential in clinical practice. This assessment should lead to adherence-enhancing interventions that must be tested on their effectiveness. Pathways to optimizing eye drop adherence are the simplification of treatment regimens (e.g. 2 daily doses or fewer), regular follow-up visits (e.g. at least every 3 months) and patient education.

CONCLUSION

It is essential to assess both structure and function in order to detect glaucoma progression. Rapidly establishing a reliable baseline is crucial in this process. A functional baseline requires repeated visual field testing with the same threshold algorithm. Documentation of the optic disc for structural baseline can be done clinically or with imaging devices. It is important to realize that these 2 methods are complementary and cannot replace one another.

Additional quantitative imaging can support the progression monitoring. Currently available imaging devices for the identification of changes in the optic disc and RNFL are HRT, GDx, and OCT.

Rate of progression provides important information about the risk of vision loss. Determination of the individual progression rate will guide clinical decision-making.

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