Monitoring the Progressing Glaucoma Patient – What Are the Challenges?

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Abstract

Diagnosing glaucoma progression is complex. It is essential to assess both structure and function to detect progression. Establishing a reliable baseline is crucial in this process. A functional baseline requires repeated visual field testing. Documentation of the optic disc appearance is necessary for the acquisition of the structural baseline. This can be achieved by the complementary modes of both clinical and imaging device-based optic disc documentation. Imaging-based methods to assess progression and rate of progression are likely to prove important in the future, but currently more guidance for their use in clinical practice is required. Rate of progression provides important information about the risk of vision loss. Guidelines therefore recommend determining the rate of progression for the individual patient when planning management. Adherence issues need to be addressed before changing treatment strategy, since poor compliance may play a considerable role in the progression of disease in many patients. 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.

Keywords

Glaucoma, progression, visual field, stereo photography, confocal scanning laser ophthalmoscopy (CLSO), Heidelberg Retina Tomography (HRT), glaucoma detection system with variable corneal compensation (GDx VCC), optical coherence tomography (OCT)

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Glaucoma is a chronic, progressive optic neuropathy mostly associated with elevated intraocular pressure (IOP).[1] Without adequate management, glaucoma can lead to reduced quality of life (QoL) and irreversible visual loss.[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 of 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 tailored to the individual patient. The goal of glaucoma treatment is to maintain the patient's visual function and related QoL at a sustainable cost in terms of inconvenience, side effects and financial implications.[3]

Detection of Progression

Definitions

European and US guidelines describe progression as a worsening of structural and/or functional defects.[3,4] However, more detailed definitions of progression have not yet been established. It is well-known that progression can occur at normal IOP levels; therefore, we cannot rely on tonometry alone. It is essential to assess both structure and function to detect progression. It was generally accepted that optic disc changes precede visual field (VF) damage.[5] However, the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS) have shown that structural and functional damage seldom overlap in patients converting from ocular hypertension (OHT) to glaucoma,[6,7] and that VF changes may precede optic disc damage. The same was shown in glaucoma patients with progression.[8–10]

Both optic disc photos/digital imaging and VF are complementary to monitor change, and VF is probably not the ideal gold standard to validate imaging devices. Statistically significant structure–function correlations exist only in patients with advanced glaucoma.[11] In terms of the definitions of structural defects, the European Glaucoma Society (EGS) Guidelines describe clinical optic disc assessment, but the analysis is subjective.[3] Analysis of structural defects should ideally be both qualitative and quantitative.

In the evaluation of functional defects, the EGS has made recommendations in terms of 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 below, in the section on determining the rate of progression.

Clinical Trials Have Used Varying Criteria for Glaucoma Progression

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

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

In the Collaborative Normal Tension Glaucoma (CNTG) study,[15] the definition of VF change was based on the comparison of threshold values with baseline. Structural change was analysed by masked assessment of stereo photographs.

Various Tests Detect Progression in Different Patients

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

Heidelberg Retina Tomography of the Optic Disc

Confocal scanning laser ophthalmoscopy (CSLO) with the HRT has the longest track record to detect and monitor structural glaucoma progression. Since its release 15 years ago, the operational hardware and software have continuously been modulated, yet have remained 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 by >10% from baseline.[17] Topographical change analysis (TCA) is independent of the contour line and reference plane and is probably more reliable to assess structural progression with the HRT.

Kourkoutas et al., in a report with 54 patients, tried to identify the discrepancies between HRT-defined progression with TCA and progression detected by expert-assessed sequential disc stereo photographs.[18] A smaller proportion of eyes progressed by stereo photograph assessment alone (6%, or three eyes) compared with isolated HRT-defined progression (30%, or 16 eyes). Progression on exclusively 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 harder to assess on photography. These findings confirm that HRT and stereo photographs are complementary in the follow-up of a glaucoma patient.

Glaucoma Detection System with Variable Corneal Compensation of the Retinal Nerve Fibre Layer

A study by Medeiros et al.[9] evaluated the ability of scanning laser polarimetry to detect progressive RNFL loss in glaucoma patients and patients suspected of having the disease. Three hundred and fifty-five eyes from 195 patients were included with a mean follow-up of four 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 (guided) progression analysis (GPA) of SAP.

Over time, 10% showed progression by stereo photographs and/or SAP. Of those, 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 the progressors and the non-progressors. However, the rate of decline was significantly higher in the progressing group compared with the non-progressing group (p=0.001).

Optical Coherence Tomography of the Retinal Nerve Fibre Layer

Leung et al. assessed structure (RNFL) by OCT.[19] Seventy-two eyes from 41 patients were included in this study with a follow-up of more than three years. Stratus OCT and SAP were performed annually. Progression was determined by GPA for average RNFL thickness and by linear regression between mean deviation of SAP and age. Sixteen eyes showed progression on OCT and nine on SAP. Only seven eyes showed progression on both OCT and SAP. They concluded that there was poor agreement between progression by OCT (RNFL) and SAP. These results once more emphasise 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.[3] Functional assessment requires repeated VF tests to overcome the learning effect. The first documentation of a VF defect should be confirmed as soon as possible on at least two additional consecutive exams. A series of reliable VFs with more than minor fluctuation in mean deviation suggest progression. However, the VF in stable severe glaucoma shows more fluctuation compared with stable mild glaucoma.[20]

Structural assessment requires documentation of optic disc appearance. Colour photographs are almost identical to what is observed during clinical examination, yet they are magnified and can be compared with previous images. Stereoscopic photographs (ideally simultaneous with fixed angle) are the preferred method in qualitative imaging. Images obtained with digital scanning devices are dependent on software for interpretation. Frequently, 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 the Identification of Changes in the Optic Disc and Retinal Nerve Fibre Layer

As mentioned above, optic disc photographs are the gold standard in the structural assessment, but changes can be difficult to identify and time-consuming.[3] Furthermore, there is large inter-observer variability and quantification of changes remains a difficult task. Additional quantitative imaging can support the progression monitoring. Digitised quantitative imaging is likely to prove important in the future to assess progression and rate of progression.

Artes et al.[21] investigated the relationship between VF and HRT change in a prospective longitudinal study with 84 patients and 41 healthy controls. At intervals of six months, all participants received SAP, high-pass resolution perimetry (single-reversal 'staircase' technique) and HRT. During follow-up, change manifested either predominantly in the VF or predominantly in the optic disc. Few patients showed disc and VF change to the same degree. However, Strouthidis et al.[22] 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. They concluded that there was 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 in terms of which machine is 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 they will never replace a meticulous clinical examination.

Determining the 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. Line A in *Figure 1* represents the effect of ageing alone on ganglion cell loss. "The patient identified by line B is worsening due to disease, but might not need treatment, while those following lines C–G will be disabled within their lifetime unless successfully treated."[3]

Regular Visual Field Assessment Is Recommended to Identify the Rate of Progression

Evidence-based guidance on the frequency of VF examinations required to identify clinically meaningful rates of change in glaucoma appeared only recently.[23] *Table 1*[23] illustrates that three examinations per year are required to identify an overall change in mean deviation (MD) of 4dB over two years in a patient with average VF variability. From these results, the recommendation can be deduced to perform three VFs (SAP) per year in the first two years of follow-up. Subsequently, the rate of VF progression can be assessed. Afterwards, one VF per year is sufficient, with a control VF if any change is suspected. "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] It is important to stress that non-conventional perimetry (e.g. frequency doubling technology and short wavelength automated perimetry) can support but not replace SAP.

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 now been replaced by faster

Figure 1: Evaluation of Whom to Treat[3]

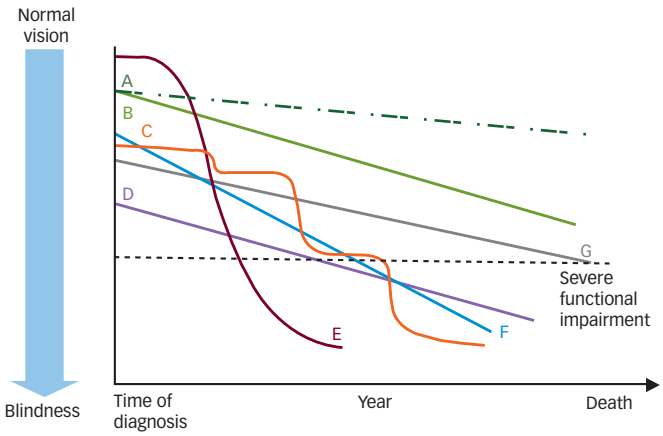

Table 1: Rates of Visual Field Change[3]

Progression Rate (dB year)			
A: Total MD change (dB)	2 years	3 years	5 years
-1	-0.5	-0.3	-0.2
-2	-1	-0.7	-0.4
-4	-2	-1.3	-0.8
Annual Examinations			
B: Total MD change (dB)	2 years	3 years	5 years
-1	7	6	4
-2	5	4	3
-4	3	3	2

Rates corresponding to total change in mean deviation over two, three and five years (A) and the number of visual fields per year required to detect the corresponding change with 80% power (B). MD = mean deviation.

algorithms. The standard strategy for Humphrey automatic perimetry (HFA) is Swedish interactive threshold algorithm (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 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 fewer than four stages (e.g. 32 test locations in two stages) can be used for screening (±3-minute testing time). However, four stages (59 test locations) are more appropriate when following up VF damage. Tendency-orientated perimetry (TOP) is another fast algorithm from Octopus that can be used for screening purposes.

In glaucoma the VF is performed in the central 24º field, in correlation with the distribution of the majority of retinal ganglion cells. This corresponds to the 24–2 programme for HFA and the G1/G2 programme for the Octopus. Compared with the 30º programs (30–2 for HFA or 32 for Octopus), there is only a small reduction in information, but fewer artefacts.

Computer-assisted progression determination exists in two modes: it can be event- or trend-based.[3] The event-based mode is designed to determine whether the VF has progressed compared with baseline (e.g. glaucoma change probability maps [GPA]) These programmes require a minimum of five tests to exhibit likely progression.[3] By contrast, the trend-based computer-assisted mode is designed to determine rate of progression (e.g. Peridata and Progressor for point-wise linear regression analysis, or EyeSuite and GPA for linear regression analysis of the indices).[24–28]

Progression and Adherence

Following progression detection, subsequent management decisions are crucial. These can consist of 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 concerns need to be addressed. The investigation of Vandenbroeck et al.[29,30] 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. Forty per cent of glaucoma patients admit to missing >1 doses in the last two weeks, and 12% admit to missing >2 doses in the last two weeks. 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 in terms of their effectiveness. Pathways to optimising eye-drop adherence are the simplification of treatment regimens (e.g. two daily doses or fewer), regular follow-up visits (e.g. at least every three months) and patient education.

Conclusion

It is essential to assess both structure and function to detect glaucoma progression. Rapidly establishing a reliable baseline is crucial in this process. A functional baseline requires repeated VF testing with the same threshold algorithm. Documentation of the optic disc for structural baseline can be performed clinically or with imaging devices. It is important to realise that these two methods are entirely complementary and will never 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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