Abstract

The detection and diagnosis of glaucoma is only the beginning of a long journey for doctor and patient. Once the appropriate diagnosis is made, deriving the initial treatment protocol may be complex, but not nearly as challenging as carefully and patiently monitoring the progression of the disease process over several years while crafting effective treatment strategies intended to minimize visual function loss through determined slowing of the progression of the disease. Technology to monitor progression through structural change evaluation has become complex and expensive and the experienced and skilled clinician is essential when navigating the various technologies to the patient’s advantage. This article discusses risk factors for progression of glaucoma, and reviews some of the functional and structural parameters that may indicate progression.

Key words

Glaucoma progression, risk factors, functional, structural

Introduction

The detection and complicated diagnosis of glaucoma is only the beginning of the long journey for the doctor and the patient. Once the diagnosis is made, there may be some complexity in developing a treatment regimen for the patient. However, it is not nearly as challenging as monitoring the progression of the disease process over several years while crafting an effective treatment strategy intended to minimize visual function loss through determined slowing of the progression of the disease. Collaboration, expertise training, research and technology are the key factors as we continue to search for a cure for this disease. The World Glaucoma Association in their 8th Consensus meeting held in Paris,
France, in June of 2011 published summary consensus points on the progression of glaucoma. Much of their collaborative and disseminated work is quoted in this article.¹

The average duration for the disease is estimated as being about 15 years with durations as long as 30-40 years possible.² Constant monitoring of the visual field, the optic nerve head and the retinal nerve fiber layer is essential in the evaluation of the progression of the disease.³ The disease progression must at each visit be staged as improved, stable or progressed.²,³ If progression is noted, steps should be taken to confirm the progression. Sadly, simply reducing the intraocular pressure in glaucomatous eyes does not halt progression completely and research into alternative treatments abound.⁴

In years past the clinical judgment and expertise of the clinician, albeit subjective, was one of the most powerful weapons in the glaucoma arsenal. With the introduction of advanced imaging and interpretive technology, objective quantification for the purposes of both diagnosis and progression of glaucoma has improved while the complexity and expense of the progressive technology and research has skyrocketed. Technology to monitor progression through structural change evaluation has become ubiquitous. These technologies are not interchangeable with each other or even comparable on an apples-to-apples level. Some statistical analysis packages are proprietary and without explanation their algorithms require a leap of faith that the technology will be around 30 years from now to continue the monitoring of progression over time and that changes in the field will not lead to redundancy and incompatibility of the hardware and software with current technology.¹ That’s a tall order by any measure.

Clinical decision making is certainly benefitted by obtaining information with multiple test modalities, even if they often do not fully correlate. Most of the methods to evaluate glaucomatous field progression agree only 50-60 percent of the time.³ Multimodal investigation should not sacrifice the quality and frequency of the standardized protocol selected for monitoring progression in a particular patient but can on occasion be informative. Additional information may be obtained utilizing alternative strategies and technologies but care must be taken to ensure these technologies and algorithms are supported by evidence-based research to reliably study the rate of progression.¹ Glaucoma care of our patients will truly benefit when the technologies are able to fully integrate and relate to each other.

The risk factors driving glaucoma progression

Risk factors for progression are identified and carefully considered in the progression of glaucoma so that the potential harm from that particular risk factor, if modifiable, could be minimized. Furthermore, the strength of the clinical risk factor should be taken into account in aggressiveness of treatment and scheduled follow up, in addition to calculating risk/benefit profiles. Risk calculators are helpful indicators, but clinically not definitive.¹

Ocular hypertension is a strong risk factor for progression, indicating the necessity of medical intervention and increased frequency in follow up.¹,⁴ Higher IOP is a known strong risk factor for progression, as are thin corneas in patients with high baseline IOP.¹ In addition to the increased IOP, the variability of the diurnal pressure should also be considered a risk factor specifically for predicting progression in normal tension glaucoma.⁴

The rate of deterioration is predictable by race. Caucasian, Hispanic and Chinese patients with open-angle glaucoma lose approximately 1.1dB of sensitivity per year to progression, while in patients of African descent the rate is significantly higher.² Progression is therefore fairly and resolutely predictable: for Europeans 1.1dB loss for the average duration of 13 years would be 15dB, which represents about one half the visual field of one eye.²

Family history of glaucoma is associated with higher risk for progression as are findings such as pseudo exfoliation, disc hemorrhage, lower ocular perfusion and increased age.⁴,⁶ The elderly population affected by glaucoma is also at risk for
other ocular, systemic and neurological conditions that contribute to the presentation of the structure of the optic nerve and retinal nerve fiber layer and the functional aspect of the visual field at any given time. ³

The importance of the various risk factors may change as the disease changes from early to moderate and from moderate to severe. Progression of optic disc damage in treated patients is more likely to progress in eyes with advanced glaucomatous rim damage and damage to the para-papillary tissue. This progression was found to occur independently of IOP. ⁴

In addition to the complexity of monitoring glaucomatous progression, the clinical practitioner of today has to weigh several factors. This might include clinical assessment, structural measures and functional evaluation in addition to ocular and neurologic history, genetic factors, treatment and systemic health of the patient. ³ Enter the highly skilled and experienced clinicians faced with the long-term care of the patient with glaucoma. The war against glaucoma is long-term and strategically fought over many years.

**Functional change indicators of progression**

Progression can be monitored in terms of functional or structural changes. In order to consistently monitor progression in the functional arena, visual field changes using standard white on white perimetry of at least the central 24 degrees using a non-matrix target is considered preferable and the standard of care within the profession. ¹ A reliable baseline must be established by at least two visual fields utilizing the same protocol in the period of the first six months following diagnosis. ¹ The rate of visual field progression is used to guide the therapeutic intervention for the individual patient. The rate of progression in treated eyes is assumed to be linear in the global indices such as mean deviation and, the visual field index (VFI) is used as a summary of visual field damage. The VFI is a helpful trend based analysis plot of the remaining vision over time, taking into consideration the patient’s age. Both are good indicators, but utilizing the VFI in early damage might serve to underestimate the damage due to the reliance on the pattern deviation probability maps. ⁷ The program weights the central visual field more heavily. In addition, global indices might miss focal progression, and pattern deviation may underestimate the progression. ¹

In patients at high risk for vision loss or with damage, the frequency of the visual field should be increased to at least three fields in six months. ¹ The visual fields should be evaluated for reliability and high positive false errors, rim artifacts or patient learning curves. ¹ Visual fields with false positives that exceed 15 percent are not useful for interpretation, and rates lower than 15 percent are not necessarily reliable either. ¹ Once the test protocol is established, it should remain stable throughout all the evaluations to establish the progression rate. Test variability can be reduced using proper set up of the visual field measurement and careful training and monitoring of the patient by the technician. ¹ Careless visual fields are destructive to the monitoring process. Not only does it waste an opportunity for time sensitive observation for progression, it adds noise to the already difficult to discern pattern.

The visual fields should be repeated close to every 6-9 months after the initial baseline has been established. ¹ Low and moderate risk patients should have at least one visual field evaluation per year provided they are stable and not progressing. If a field raises suspicion of progression, the field should be repeated to confirm the progression. ¹ The visual field is then repeated every 3-4 months over a period of two years to determine the rate of progression. A loss of 2dB/year or more is considered rapid progression. ¹ It is important to recognize that visual field sensitivity is measured in decibels using a logarithmic number, while the number of ganglion cells lost is a non-logarithmic number. ²

“Event” analysis by the Humphrey Event analysis, such as indicated by the Glaucoma Change Probability and Glaucoma Progression analysis software from Carl Zeiss Meditek, might prompt suspicion of functional progression. ³ The event analysis by the software is prompted by a change from baseline that exceeds a set threshold. ¹³ Event analysis is more
useful when there are fewer visual fields that could be used for serial analysis. Such events usually should trigger two more visual fields to confirm the change. Clinical findings or “events” that may prompt suspicion of progression could include objective findings such as optic nerve and retinal nerve fiber layer evaluation by imaging or a finding of uncontrolled IOP. Therefore, theoretically, each time a patient becomes therapeutically non-compliant it represents an “event” and should trigger two or more fields. High risk findings such as splinter hemorrhages at the disc are strongly suggestive of high risk for progression. High risk patients should have visual field exam frequency of at least two visual fields per year and more often if progression is suspected. Risk profile is additionally established by rate of progression and the stage of disease. Taking into consideration the event analysis, it is up to the clinician to determine and interpret the reliability of the baseline fields, determine the rate of progression, and the confidence interval and the severity of the visual loss. A new baseline should be established when therapeutic intervention is initiated or is adjusted.

Total deviation analyses tend to detect progression earlier than pattern deviation and pattern deviation alone may underestimate the true glaucomatous progression. Trend analysis, such as Moorfields regression analysis, trends the magnitude of change over time. It evaluates the visual field results that have been collected over time for interpretation with linear regression. One of the criticisms of this technique is that visual loss is not necessarily linear. Rate based analysis is used when a larger number of visual fields are available to accurately determine the rate of progression. It usually takes a period of more than two years to determine the rate of progression and it is interpreted using a calculated confidence limit.

**Structural change indicators of progression**

Subjectively estimated CD ratios and color drawings, in an attempt to follow progression, is of low value due to inter-observer and intra-observer differences. Serial optic disc stereo photographs are used to measure structural progression when comparing findings to a baseline photograph. Splinter hemorrhages and para-papillary changes, especially the increase in Beta zone para-papillary atrophy that may indicate stronger risk for progression, can be identified and followed with color photography.

Confocal scanning laser, scanning laser polarimetry and optical coherence tomography provide the opportunity to perform reproducible, objective measurements of the optic disc and retinal nerve fiber layer. Some variability can naturally be expected. The visibility of the disc margin, the accuracy of the segmentation algorithms and the variations in vascular blood volume are a few of the factors to be considered. Image quality can negatively affect the interpretation and should be carefully reviewed by the clinician for reliability. More than one image might be needed to build an acceptable baseline. Some instruments acquire several images to construct the baseline at a single encounter. There is similar reproducibility between the various instruments but consensus about the reproducibility across disease severity has yet to be reached.

Event and trend based analyses may suggest structural change. Rates of change between optic disc, retinal nerve fiber layer and macular parameters may vary from each other. The quantitative assessment of the optic disc and retinal nerve fiber layer are useful parameters for change detection when using the same technology. Using different technologies and scan protocols could influence the detection of progression, they are not necessarily interchangeable. The jury is still out on how useful macular measurements are for detecting change in terms of progression.

When determining the effect of aging on the measurements over time the use of longitudinal data to determine age-related change is more reliable than extrapolation from cross sectional data and should be considered when using age based norms in software interpretations. We are capable of measuring changes with the technology available today that may not necessarily be of any clinical relevance. The bottom line is that structural change is predictive of future functional loss, no matter how we measure it.
The frequency of imaging testing should be determined by the severity of the individual’s disease and the speed of the progression of the disease and certainly should not be dictated by what is covered by the patient’s insurance. Some longitudinal studies have performed imaging annually and in some cases up to three times per year in order to detect progression.¹

**The marriage of structure and function**

We have always been certain that function follows structural change, but recent research has shown that functional changes can occur without any measurable structural changes that can be detected. SWAP perimetry may indicate change or progression before technology such as the Heidelberg Retina Tomograph can measure the structural change.³⁹¹⁰¹¹ Using only functional testing, progression could be underestimated in early glaucoma.

Estimation of progression using structure and function may not always give the same indicators of progression. Function-structure correlations can only be detected 50 percent of the time.¹¹ Progression is more difficult to determine in eyes with advanced field damage. Optic topography changes, changes in the retinal nerve fiber layer or para-papillary changes will often occur or be measureable before changes in the white on white visual field can be noted in patients with ocular hypertension or the glaucoma suspect.¹

**Conclusion**

The strategic long-term evaluation of progression of glaucoma is an evolving field of multimodal study. The combination of both structure and function should be evaluated when following the eye for glaucomatous progression and must be weighed with the risk factors each unique patient brings. Constant collaboration and research is needed to make the best possible decisions for our patients with glaucoma.
7. Artes PH, Nicolela MT, LeBlanc RP, Chauhan BC. Visual Field progression in glaucoma: total versus pattern deviation analyses. 46(12) 4600-4606 December 2005

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1) With each patient visit you should establish whether the glaucoma’s progression is________.  
   A. Stable  
   B. Deteriorated  
   C. Progressed  
   D. Improved  
   E. A, C, or D.

2) The variability of the diurnal pressure should be considered a risk factor for predicting progression in normal tension glaucoma.  
   A. True  
   B. False

3) Glaucoma progression can be monitored in terms of __________ or ______________ changes.  
   A. Functional or structural  
   B. Progressing or deteriorating  
   C. Visual field or focal  
   D. Pattern or visual field

4) What type of analyses tends to detect progression earlier?  
   A. Pattern deviation  
   B. Total deviation

5) The constant monitoring of what elements is essential in the evaluation of the progression of glaucoma?  
   A. Visual field  
   B. Optic nerve head  
   C. Retinal nerve fiber layer  
   D. All of the above

6) Caucasian, Hispanic and Chinese patients with open-angle glaucoma lose approximately 1.1dB of sensitivity per year to progression. Which race is the rate of loss significantly higher?  
   A. Pacific Islander  
   B. Mongolian  
   C. African  
   D. None of the above

7) In patients at high risk for vision loss or with damage, the frequency of the visual field should NOT be increased.  
   A. True  
   B. False

8) What percentage of the time do most of the methods to evaluate glaucomatous field progression agree?  
   A. 50-60  
   B. 70-80  
   C. 80-90  
   D. 85-95

9) A loss of __dB/year is considered rapid progression.  
   A. 1  
   B. .5  
   C. .25  
   D. 2

10) The frequency of imaging testing should be________.  
    A. Determined by the severity of the individual’s disease  
    B. Determined by the speed of the progression of the disease  
    C. Should be dictated by what is covered by the patient’s insurance  
    D. A & B  
    E. None of the above