Glaucoma is a chronic progressive optic neuropathy that results in damage to retinal ganglion cells and surrounding tissue structures. The most common form of this disease, primary open-angle glaucoma, is generally associated with elevated IOP, which produces pathophysiologic damage to the optic nerve. The main goal of medical or surgical treatment is to lower the IOP to a level that prevents or reduces further loss of visual function. When determining how best to manage patients with glaucoma, physicians must consider many clinical factors, including visual field status, the optic disc’s appearance, IOP level, patients’ adherence to and persistence with prescribed therapy, their medical history, their family and social history, and the constancy of these factors over extended periods of follow-up. Key to management is whether the patient’s visual status appears to have improved, worsened (progressed), or remained stable. Evaluating the peripheral visual field, optic nerve head, and retinal nerve fiber layer (RNFL) is important at this juncture and is the primary focus of this article.

Many textbooks provide seemingly straightforward examples of progressive glaucomatous damage to the visual field and optic nerve head. As an example, Figure 1 presents annual optic disc photographs of the left eye of a glaucoma patient taken over the course of 6 years. During this period, the inferior portion of the neuroretinal rim thins, and blood vessels become displaced.

Figure 1. Annual photographs of the optic disc of the left eye of a patient with glaucomatous progression over 6 years. Note the thinning of the neuroretinal rim inferiorly and displacement of blood vessels during that time period.

Figure 2. Standard automated perimetry for the left eye of the same patient whose optic disc photographs are shown in Figure 1. The visual field results indicate the initial presence of a superior nasal step that progresses to become a superior arcuate nerve fiber bundle defect.
Likewise, the series of six visual fields shown in Figure 2 reveals a corresponding superior nasal step that becomes a full superior arcuate defect, indicating a strong relationship between structural and functional changes over that 6-year period.

Although this connection is what most clinical practitioners hope to see, the relationship between structural characteristics (the appearance of the optic disc and RNFL) and functional capabilities (perimetry and other clinical psychophysical tests) that are affected by glaucomatous damage can vary considerably. Historically, many studies have indicated that structural glaucomatous changes can be observed clinically before any evidence of functional loss using available diagnostic procedures.1 Recent investigations have reported the opposite: functional glaucomatous deficits can occur before structural changes.2-4 In 2007, Hood and Kardon4 presented a model of glaucomatous damage illustrating that either order can occur and that structural changes will be observed before functional alterations in the majority of instances. Correlations between structural and functional changes produced by glaucoma can only be realized in 50% or fewer of cases, even when highly sophisticated diagnostic and analytic procedures are employed.2-7

An example of discordance between structure and function in glaucoma is presented in Figures 3 and 4. Optic disc photographs and images from the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany) indicate normal optic discs (Figure 3). The results of standard automated perimetry and short wavelength automated perimetry (SWAP), however, indicate inferior arcuate nerve fiber bundle defects indicative of glaucomatous damage in both eyes (Figure 4).

These examples and the literature cited illustrate just a portion of the information that clinicians must evaluate and the diagnostic dilemma they face when attempting to determine whether a patient’s condition is improving or if his or her glaucoma is stable or worsening. This article provides an overview of glaucomatous progression. Its emphasis is visual field determinations and assessments of the optic disc and RNFL, but the piece also discusses the tools that are currently available and the need for future developments and refinements.

Figure 3. Optic disc photographs (top images) and HRT results (bottom images) for the left and right eyes of a patient with glaucomatous visual field loss. Both the photographs and HRT findings indicate that the optic nerve head is within normal limits.

Figure 4. Standard automated perimetry (top images) and SWAP results (bottom images) for the left and right eyes of a patient with glaucomatous visual field loss. Both standard automated perimetry and SWAP indicate inferior arcuate visual field loss in both eyes.
VISUAL FIELD PROGRESSION IN GLAUCOMA

Virtually every multicenter clinical trial in glaucoma has used different criteria for defining glaucomatous visual field progression.\(^8\) A summary of these procedures and a comparison of their relationships to each other can be found in several key articles.\(^8\)\(^-\)\(^11\) Multiple laboratories have demonstrated meaningful differences in the specificity, sensitivity, time of onset, and computational complexity of various methods to evaluate glaucomatous visual field progression.\(^8\)\(^-\)\(^11\) Moreover, these methods agree with each other only about 50% to 60% of the time.\(^8\)\(^-\)\(^11\) In many cases, therefore, one procedure will indicate glaucomatous progression, and another will indicate stability. As a consequence, no consensus has been achieved regarding the best or most appropriate method of monitoring glaucomatous visual field progression.

It is possible to group each of the evaluative methods into one of several categories.\(^8\) Perhaps the most common approach is clinical judgment, whereby a physician uses his or her experience and prior knowledge to make a subjective determination as to whether the patient’s visual field is stable, improving, or worsening over time. Clinical judgment is flexible, it is easy to perform, and it requires no additional computation or quantitative analysis. On the downside, clinical judgment is not standardized, it varies considerably from one individual to another, and it is subjective and poorly controlled. There is a tendency for physicians, including those with great expertise in perimetry, to identify progressive visual field change too frequently, which reduces the specificity of the procedure.\(^12\)

Methods of classification have also been employed to determine visual field progression. Examples of this type of analysis include the Advanced Glaucoma Intervention Study (AGIS) and Collaborative Initial Glaucoma Treatment Study (CIGTS) criteria, in which investigators divided the visual field into specific patterns and used a scoring system from 0 (normal visual field) to 20 (blindness) to denote the various levels of glaucomatous visual field damage.\(^8\)

There are several advantages to this approach. A systematic, quantitative method can be applied in a consistent manner to all visual fields, it indicates the magnitude of functional visual field loss, and it is a relatively simple procedure to implement. Systems of classification also provide a means of indicating the severity of glaucomatous visual field loss. Brusini and Johnson published a review of different visual field classification systems.\(^13\) The disadvantages include the lack of specific information about the spatial and locational properties of visual field loss with this scoring system and the lack of information concerning the scaling of different classification intervals (eg, is the difference between 5 and 7 the same as the difference between 14 and 16?).

Event analysis compares the visual field results of a single examination (typically the current one) to prior results (usually the average of two baseline visual fields). The Glaucoma Change Probability (GCP) and Glaucoma Progression Analysis (GPA) programs (both from Carl Zeiss Meditec, Inc., Dublin, CA) are two examples of such systems.\(^14\)\(^,\)\(^15\) This approach has the advantages of being quantitative and relatively simple to implement, and it accounts for differences in variability of response associated with visual field location, threshold sensitivity value, and the patient’s age. The GPA program also requires confirmation of suspected changes and a criterion for a minimal number of visual field locations that demonstrate the change. The main disadvantages are that event analysis does not account for spatial characteristics or the shape of visual field loss, it does not consider interim results (only the current and initial visual fields), and it does not differentiate between glaucomatous and other types of visual field loss. There is an overlap, however, in the damage produced by glaucoma, other optic neuropathies, and some retinal vascular conditions, so additional information besides the visual field is necessary to establish a clear differential diagnosis.

Trend analysis evaluates all of the visual field results that have been collected over a series of sequential examinations via techniques for linear regression.\(^8\) A commercial analytical procedure known as Progressor (marketed by Medisoft Limited, Leeds, United Kingdom; intellectual property owned by the Institute of Ophthalmology [part of University College London] and Moorfields Eye Hospital NHS Foundation Trust) is available for performing this type of analysis. It uses the level of significance of changes in the slope of visual field deterioration at a criterial number of locations to determine the status of glaucomatous eyes from serial visual fields. Among its advantages, trend analysis uses all of the visual field data available, it implements special analytical techniques (eg, “three-omitting” and spatial filtering) to optimize sensitivity and specificity, and it can be applied in a simple, straightforward manner.\(^16\)\(^-\)\(^18\)

The primary disadvantage of trend analysis is that it uses a linear analysis of changes in visual field sensitivity over different time periods. If the type of visual field changes are not linear but instead episodic, exponential, or some other complex mathematical derivation, a linear analysis may not be the best method of determining potential alterations in visual function. Each method used to determine glaucomatous visual field progression has distinct pros and cons, and it is not clear which procedure is best suited for particular patients or for answering specific clinical research questions.
OPTIC DISC AND RNFL PROGRESSION IN GLAUCOMA

Traditionally, clinicians have employed various photographic methods to identify and evaluate structural alterations produced by glaucoma. More recently, scanning laser ophthalmoscopy, optical coherence tomography, and birefringence retardation techniques were developed as means of quantitatively assessing topography and other structural properties of the optic nerve head and RNFL. The techniques used to provide accurate monitoring of the optic nerve’s and RNFL’s structural properties employ methods that are essentially the same as those used for evaluating visual field progression—namely, clinical judgment, classification and staging of structural changes, event analysis, and trend analysis.

As with the findings for perimeter evaluation, each of these approaches has distinct advantages and disadvantages. Event analysis (glaucoma change probability) and trend analysis (Moorfields regression analysis) appear to be the most commonly used procedures. Many practitioners use a particular percentage of change for sectors of the optic disc using various forms of imaging technology, evaluate pointwise change of the visual field in suspicious locations, assess serial trends for both structural and functional measures, and rely on related procedures that they may have found to be helpful in their clinical management of glaucoma.

COMBINING FUNCTIONAL AND STRUCTURAL INFORMATION

One of a skilled clinical practitioner’s tasks is to make an informed clinical decision on the appropriate management of a glaucoma patient or individual at risk of developing glaucoma. Obviously, this process is quite subjective and therefore varies considerably among clinicians. It involves different strategies and methods of weighting the importance and influence of many factors.

Several investigative groups have attempted to develop more objective, quantitative methods of combining structural and functional information. The results to date provide rather convincing evidence that such a procedure would be clinically useful. This work is still in its infancy, however, and it is currently unclear exactly what information is relevant and how that information should be combined. In addition, a limited number of longitudinal data sets are available from well-controlled prospective studies, which restricts the evaluation of these procedures. Much is lacking to allow a rational, evidence-based decision regarding objective, quantitative methods of evaluating glaucomatous visual field progression. Moreover, nearly all of the procedures that have used this approach have assessed structural and functional alterations from glaucoma at the same time intervals, despite the fact that clinically observable changes in structure and function, using currently available technology, occur at different time periods in most cases.

CURRENT METHODS FOR EVALUATING GLAUCOMATOUS PROGRESSION

What should the clinical practitioner use today to assess glaucoma patients and individuals at risk of developing glaucoma? Some general guidelines can assist the evaluation of structural measures, functional evaluations, and clinical assessments. First, it is important to develop an impression from all of the information that is available for the patient. It will then be easier to distinguish between ongoing trends related to the pathophysiology of glaucoma and isolated single events that are specific to a particular clinical visit and may be unrelated to glaucoma. Also, physicians should confirm suspected glaucomatous change by repeating the test at another time, comparing it to other diagnostic and clinical results, and performing a risk/benefit assessment of the patient’s ocular status.

Clinicians should avoid relying on only one or two aspects of the clinical examination as the basis for their decisions. It is important to see the big picture concerning the patient’s ocular and medical well-being. Moreover, it is critical to determine the risks and benefits associated with the various options for clinical treatment. For example, the management of an 85-year-old with a subtle nasal step in one eye and minimal risk factors for glaucoma will differ dramatically from that of a 40-year-old with multiple glaucoma risk factors, medically uncontrolled IOP, and dense arcuate visual field defects in both eyes.

Lastly, perspectives and experiences vary among clinical practitioners. It can be helpful to get the opinions and advice of colleagues who may have experienced successful and poor outcomes with similar patients.

FUTURE DIRECTIONS FOR DETERMINING PROGRESSION IN GLAUCOMA

In the author’s opinion, five actions are important for the future refinement of methods to manage and observe glaucoma patients and the results of their diagnostic tests. The first is to improve existing signal-to-noise analyses by developing better testing procedures, implementing enhanced and more robust evaluative strategies, applying more sophisticated procedures for statistical analysis, and initiating advanced methods of extracting
subtle pathologic “signals” from data. These efforts could augment the salience of signals, diminish the influence of noise, and improve the ability of practitioners to search, find, and extract new indicators of pathologic glaucomatosus markers. Many of the techniques used for higher-level data mining and informatics could be utilized for these purposes.

Another need is to identify the optimal methods of combining information (structural, functional, clinical, historical, genetic, treatment, and other factors) into an easy-to-use computational model. Some laboratories have begun work in this area, but the effort is still in its infancy.

A third need is an improved understanding of the rate of progression in order to provide a relevant and applicable method of predicting future clinical outcomes and to produce heuristic procedures for evaluating possible interventions and modifications of treatment.

Also of importance is identifying methods to provide a diagnostic test results “signature” for glaucoma that will allow distinction between the disease’s pathophysiologic changes and those due to methodology, testing conditions, attentional and motivational components, and other nonglaucomatosus changes. Most glaucoma patients are elderly and therefore likely to have ocular, neurologic, or systemic medical conditions in addition to glaucoma. They often have some degree of cataractous or precataractous optical changes. It is necessary to be able to differentiate between glaucomatosus and nonglaucomatosus visual changes in order to tailor treatment and management. In this view, new methods of quantifying changes in the RNFL and optic disc using optical coherence tomography will be most helpful.

A final requirement is the development and validation of analytical methods for determining improvement in functional and structural characteristics as well as progression. With new innovations in various treatment strategies for glaucoma, the possibility of reversing glaucomatosus insults is becoming a viable option.

Much work by many laboratories and investigators will be needed to achieve these objectives and goals for the future. The result will be a more objective and evidence-based approach to the management and treatment of glaucoma as well as new discoveries concerning the mechanisms involved in glaucomatosus damage.

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