Chapter 1. The Role of the RNFL in the Diagnosis of Glaucoma

Introduction

Glaucoma is an optic neuropathy characterized by a loss of retinal ganglion cells and their axons, the Retinal Nerve Fiber Layer (RNFL). It is one of the leading causes of blindness in the world\textsuperscript{1-8}. Prevalence of glaucoma is on the increase as the world population ages. In the United States, experts expect that the number of glaucoma patients will increase from the current estimate of 2.5 million to at least 3.4 million by the year 2020\textsuperscript{9}.

The loss of Retinal ganglion cells in glaucoma is irreversible, therefore early detection is critical to prevent progression of the disease. A quote from Professor Robert N. Weinreb, former President of the Association for Research in Vision and Ophthalmology (ARVO) and Director of the Hamilton Glaucoma Center at the University of California San Diego, succinctly states this point, "If you diagnose glaucoma early, you can treat it early. If you treat glaucoma early, you can slow the rate of progression. If you slow the rate of progression, you prevent blindness\textsuperscript{14}.

Major risk factors for glaucoma include intraocular pressure (IOP), age, race, family history, myopia, and corneal thickness. These risk factors provide important information for the clinician when making a diagnosis. For example, African Americans are 6 times more likely to have glaucoma than Caucasians and POAG appears approximately 10 years earlier in African Americans\textsuperscript{10-13}.

Glaucoma Diagnosis

Glaucoma diagnosis is based on the assessment of intraocular pressure (IOP), optic nerve head (ONH), visual function, and less frequently the retinal nerve fiber layer (RNFL). There are certain advantages and disadvantages associated with each of these measures, ranging from the discriminating power of the measure (e.g., the large overlap between normals and glaucoma of IOP results in poor discrimination), to more practical considerations such as how easy is it to obtain high quality results that are reproducible. A central factor of any measure is whether it is subjective or objective. Methods that involve a subject's response are subjective and frequently have high variability\textsuperscript{15} and can improve with practice (e.g., visual fields). Subjective methods may also require a high level of expertise for accurate...
interpretation of the results (e.g., expert interpretation of optic disc photographs will be different from less experienced clinicians). Objective methods are less commonly used in a clinical setting. However, structural analysis with imaging devices that provide objective information is becoming more common. This type of objective method provides unique and highly discriminating information that cannot be obtained routinely (e.g., Scanning Laser Polarimetry provides RNFL information that cannot be visualized by the clinician, see Chapter 2 for more details on the principles of SLP). Structural analysis with an imaging device that provides objective measures has been recommended by the world’s leading glaucoma experts to be included in the standard exam of all glaucoma practices.

Glaucoma Diagnosis: IOP Assessment

Intraocular pressure is the number one risk factor for glaucoma. A high IOP is the hallmark for most of the glaucomas, and the treatment for glaucoma is to lower the IOP through medications or surgery. Tonometry is simple and fast, and it is one of the most heavily relied on measures for glaucoma diagnosis. However, a major limitation of IOP is that the damage threshold varies across individuals. For example, the majority of individuals with high IOP (ocular hypertensives) do not have glaucoma, and will not develop glaucoma. Conversely, other individuals will develop glaucoma, even with IOPs in the normal range (Normal tension glaucoma).

Another limitation of IOP is that the diurnal fluctuations can conceal high IOP spikes. Measuring a diurnal IOP curve can help with this limitation, but is impractical for routine clinical use. IOP assessment is also limited because corneal thickness affects the accuracy of the IOP measurement. It is known that thicker than average corneas will overestimate IOP and thinner than average corneas will underestimate IOP. Thus corneal thickness must be taken into account when measuring the IOP.

Clinical studies have found that the large overlap of IOP in healthy eyes and glaucomatous eyes limits the diagnostic accuracy of IOP for detecting glaucoma. Diagnostic accuracy is measured by calculating the sensitivity and specificity of a measure using a specific cut-off value, or more generally by calculating the area under the ROC curve (see Appendix A. for a description of sensitivity and specificity and ROC analysis). A study by Leske et al. measured the discriminating ability of IOP in a large population (the Barbados Eye study), and found the sensitivity for detecting glaucoma was 79% with a speci-
ficity of 64%. Despite the fact that IOP measurements are simple and convenient to use, and that they have a strong tradition in glaucoma care, the large difference between normals and patients in damage thresholds as well as the other limitations prevent IOP from being a sufficient diagnostic tool by itself for glaucoma.

Glaucoma Diagnosis: ONH Assessment

Optic nerve head (ONH) assessment with ophthalmoscopy, biomicroscopy and stereophotography is an important tool to detect and monitor glaucoma. This method involves the clinical examination of the ONH to detect abnormalities associated with glaucoma such as rim thinning, notching, excavation, presence of hemorrhages, large Cup/Disc (C/D) ratios or asymmetric C/D ratios (> 0.2 between eyes). The mean C/D ratio for a normal eye is 0.4, and the 97.5th percentile from the normal distribution is 0.7, therefore C/D ratios above 0.7 are indicative of glaucoma. Furthermore, the C/D ratio in normal eyes remains stable over time, therefore an observed change in the C/D ratio is also indicative of glaucoma.

Documentation of the ONH findings from ophthalmoscopy and biomicroscopy is made with drawings, which can be difficult to use when evaluating changes over time. ONH stereo-photography produces a high resolution image of the optic disc and peripapillary retina and creates a permanent record for close evaluation and future comparisons.

Limitations of this technique include the requirement of clear media and a dilated pupil. For ONH stereo-photography, a skilled photographer is needed, and the results are not immediately available. Even under ideal conditions, adequate quality can only be obtained approximately 80% of the time. ONH assessment is a subjective method, and it can be difficult to differentiate physiologic cupping from cupping due to glaucoma. Normal eyes with large optic discs will tend to have large cups which can be inaccurately diagnosed as glaucoma, and eyes with small optic discs will tend to have small cups which can be misinterpreted as normal. Also eyes with tilted optic discs, peripapillary atrophy, and myopic degeneration may be difficult to accurately assess.

Another limitation of ONH assessment in glaucoma is the poor sensitivity for detecting change over time. Once the visual field defect is moderate to advanced, detection of change with stereo-disc
photography is less satisfactory than with visual fields. ONH changes can also be difficult to detect in early glaucoma. A study by Quigley and colleagues found that in a group of ocular hypertensives who converted to glaucoma, only 19% exhibited ONH changes. The EMGT study found that only 7% of all 255 patients showed progressive changes in their optic disc during the entire 6 years of follow-up, where 53% were shown to progress by their visual fields.

In general, the sensitivity and specificity values based on ONH assessment are higher than with IOP assessment alone. The diagnostic accuracy varies depending on the specific study, however most studies report sensitivity and specificity values in the 70-80% range. Much of this variability between studies comes from the differences in the patient's level of glaucomatous damage, as well as how the ONH was assessed. Also, the ONH evaluation in these studies was conducted by highly trained and experienced glaucoma experts using good quality photographs. In a common clinical setting, where the quality of photographs may not be optimal and the clinician may not have the same experience as these experts, the actual sensitivity and specificity values may be lower.

Glaucoma Diagnosis: Visual Field Assessment (SAP)

In addition to IOP and ONH assessment, visual field testing is included in standard clinical examinations. The visual field is generally assessed through standard automated perimetry (SAP). Many clinicians consider the visual field test to be the 'gold standard' for glaucoma diagnosis, and they wait until the visual field shows a defect before diagnosing glaucoma. However, there is strong evidence suggesting that by the time there is a visual field defect on SAP, the disease is already in the moderate to advanced stage.

Histological studies have found that as many as half of all ganglion cells can be lost before a defect is detected by the visual field. A recent report from the OHTS study found that of the ocular-hypertensives who converted to glaucoma, only 50% had visual field defects. Numerous other studies provide strong evidence that structural abnormalities are present before visual field damage is detected with SAP.

Another important limitation of visual field testing is the high variability of the results. For example, the OHTS study found that 86% of defects detected with SAP were not replicated on repeat
testing. This led the scientists in the study (and many clinicians in their practices), to require that a defect be replicated on a second and/or third follow-up test before it was confirmed as an actual defect. This policy would push back the detection of the disease even further if a repeatable visual field defect measured by SAP is required for diagnosing glaucoma.

More specialized visual field tests such as Short-Wavelength Automated Perimetry (SWAP) and Frequency Doubling Technology (FDT) may be able to detect earlier loss by isolating specific sub-populations of ganglion cells. However there are limitations associated with these tests as well. For example, SWAP has high variability and is especially difficult for older individuals due in part to the yellowing of the lens with age. Also, all visual functional measures are inherently variable due to the subjective nature of the test.

The sensitivity and specificity reported for SAP is generally not as good as expert grading of stereo optic disc photographs. Wang et al. found sensitivity was 70% and specificity was 67% using SAP. A complicating factor of this, however, is that determining sensitivity and specificity from SAP defects is problematic when defects presented on SAP are the criteria for defining glaucoma (unless the appearance of the optic disc is used to define the disease).

In summary, current diagnostic tools have inadequate sensitivity and specificity for glaucoma detection. Furthermore, early glaucoma is often missed if the clinician relies mainly on the visual field and IOP. Subjective assessment of the ONH even with stereo-photography has limitations as well, including the requirement of a clear media and dilated pupil and a high level of expertise when evaluating the photographs. Also, accurate glaucoma diagnosis is more difficult with small and large optic discs.

**Glaucoma Diagnosis: RNFL Assessment**

RNFL assessment for glaucoma diagnosis and follow-up has several distinct advantages over current diagnostic approaches. It was demonstrated over 30 years ago that RNFL defects are the earliest sign of glaucoma. Since then, numerous studies have found that RNFL defects occur prior to visual field loss. A study by Sommer et al. found that 88% of ocular hypertensives who converted to glaucoma had RNFL defects at the time the visual field defect was detected with SAP. Furthermore, 60% of these converters had RNFL defects present 6 years prior to the visual field defect.
There is also evidence that RNFL changes can occur even prior to optic nerve head changes. A study by Quigley et al.\textsuperscript{24} found that RNFL changes are detected more frequently than ONH changes in eyes that converted from ocular hypertension to glaucoma. In a sample of 813 ocular hypertensives followed for over 5 years, they found that of the 37 eyes that developed abnormal visual field tests at the end of the 5 year period, 73% had either a RNFL defect initially or developed one during the follow-up. Progressive RNFL atrophy was observed in 49% of the eyes, while optic disc change was observed in only 19%. Several other studies also found evidence that RNFL evaluation is more sensitive for predicting future visual field loss compared to ONH evaluation, and that the RNFL is a better predictor of damage than C/D ratio\textsuperscript{33,41-44}. A study by Airaksinen and Alanko found that RNFL defects developed in 83% of early glaucoma patients, while only 42% developed an abnormal C/D ratio\textsuperscript{41}.

One method of RNFL assessment is red-free RNFL photography. This method provides high-resolution monochromatic images of the RNFL. Focal wedge-shaped defects can often be detected with this technique, however diffuse RNFL loss, which is more common\textsuperscript{45}, is more difficult to detect. Other limitations of red-free RNFL photography include the requirement of a clear media, dilated pupil, skilled photographer, and as in the case with optic disc photography, the results are not immediately available. Image quality is another important factor. Even with a skilled photographer, it can still be difficult to obtain good quality photographs routinely. Due to these limitations, red-free RNFL photography is used mostly in academic centers and is not commonly used in standard clinical practice. The sensitivity and specificity reported for red-free RNFL photography was found to be slightly higher on average than with ONH assessment. Studies using red-free photography generally find sensitivity and specificity in the range from 70-80\% \textsuperscript{46-48}. Airaksinen et al.\textsuperscript{49} found somewhat higher values, with a sensitivity of 94\% and specificity of 83\%.

In summary, evaluation of the RNFL is important for glaucoma diagnosis as RNFL damage often occurs earlier than can be detected with visual fields and even before optic nerve head damage. Red-free RNFL photography has many advantages, but the subjective interpretation of the results and the practical limitations of the method limit its usefulness.
An objective method to assess the RNFL is through scanning laser polarimetry. The GDx VCC is a scanning laser polarimeter that measures RNFL thickness using polarized light\textsuperscript{50} (see Chapter 2 for details). The GDx VCC provides objective RNFL information that is compared to an extensive normative database (see Chapter 3 for details). Comparisons to the database provide the clinician with information regarding the status of the RNFL with respect to a large number of healthy eyes of the same age. Deviations from the normal range are clearly presented, simplifying interpretation. Reproducibility of the GDx VCC has been shown to be excellent\textsuperscript{51,52}, providing the foundation for detection of small changes over time due to progression of the disease. Recent studies also show that the device has excellent diagnostic power. Reus and Lemij recently reported the GDx VCC had a sensitivity of 89\% and a specificity of 98\%\textsuperscript{53}. Furthermore, Medeiros et al.\textsuperscript{54} found that the GDx VCC was more accurate in detecting glaucoma than expert grading of red-free RNFL photographs. The GDx VCC is also very practical; the exam is very fast and simple. This helps reduce operator influence and eliminates the need for experienced technicians. As RNFL analysis enables the clinician to diagnose glaucoma early, and therefore treat glaucoma early and prevent progression, the GDx VCC will become a key tool for glaucoma diagnosis and management.

**Summary.** Glaucoma is characterized by a loss of retinal ganglion cells and their axons, therefore, assessment of the optic nerve fibers is critical for early detection and monitoring change over time. The current diagnostic tools are inadequate, and more emphasis on RNFL evaluation is needed. RNFL changes precede visual field loss\textsuperscript{33-37} and optic disc changes\textsuperscript{24,41}. Considering the difficulty of the clinical examination and the limitations of red-free RNFL photography, a simple and more objective tool for RNFL evaluation is needed. The GDx VCC provides unique, accurate and reproducible RNFL information. It is simple to use and is easy for both the patient and operator. Results are presented in a clear and concise format, simplifying interpretation. However, the GDx VCC is not intended to replace the more traditional methods of a standard clinical examination: measuring IOP, assessing the optic disc, and visual field testing. Rather, the GDx VCC should be added to the standard clinical examination to complement the information from these other methods. When the results of the GDx VCC are combined with the information gained from IOP, optic disc assessment, and visual field results, the outcome will be a more accurate assessment of the health of the RNFL.