Special Issue

Detection and Diagnosis of Glaucoma: Ocular Imaging

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Imaging is a valuable tool in the assessment of glaucoma and glaucoma progression. Although glaucoma is a clinical diagnosis—there is no blood test or definitive genetic test, for example, for the disease—the diagnosis has traditionally been subjective albeit based on certain physical characteristics of the patient. Over the years, the diagnosis has gone from a hard, blind, painful eye; to palpation indicating a hard eye associated with sudden pain or slow, painless visual loss; to a specifically described progressive optic neuropathy with characteristic neural damage and visual loss, sometimes associated with elevated intraocular pressure (IOP).

In the mid-19th century, Helmholtz and Von Graefe enabled clinical assessment of the optic nerve head (ONH); later, fundus photography permitted objective recording of this physical parameter.[1,2] Nevertheless, despite objective photographs of the ONH, subjective interpretation on the part of the clinician was necessary for identification of glaucomatous damage or progression. Different clinicians would provide discrepant interpretations of the optic nerve, and even the same observer would frequently characterize the disc differently on separate viewings of the same photograph.[3]

Measurement of ocular function is and has been similarly crude and subjective. From discriminating finger movement in different quadrants to discerning white objects on a black background to map the visual field in tangent screen perimetry, the patient must tell the examiner when a light or object is seen. The same is true of kinetic and static perimetry, both manual and automated. The patient must detect the object (or light) on the retina, realize that a light or object has been seen, and then inform the examiner of this fact. The evaluation is difficult as best, often tedious, and fraught with problems in reproducibility of findings.

For these reasons, clinicians, scientists, and engineers have sought to objectively measure optic nerve structure and function both quantitatively and reproducibly, preferably without the requirement for patient input. In the assessment of optic nerve function, this has meant multifocal electroretinography,[4] pattern electroretinography,[5,6] multifocal visual evoked potential, and pattern visual evoked potential,[7,8] among other tests.[9] Unfortunately, none of these objective functional tests has been validated to the level of perimetry, which remains the clinical gold standard, despite its shortcomings.

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Automated objective, quantitative characterization of the optic nerve has been more successful. As mentioned above, the first step in this direction was optic nerve photography, particularly stereoscopic disc photography. This method enables objective recording, but still requires subjective interpretation. More sophisticated techniques, invented and/or developed in the past quarter century, include confocal scanning laser ophthalmoscopy (CSLO), scanning laser polarimetry (SLP), and optical coherence tomography (OCT). These systems capture, in different ways, objective, accurate, and precise quantitative information about optic nerve and retinal structure that does not require subjective input for measurement. Although there is objective image and segmentation algorithm quality evaluation, subjective quality assessment is still necessary to ensure that the image acquired is adequate for evaluation and that the analysis algorithm has functioned properly.

What Can We Accomplish with Ocular Imaging in Glaucoma?

Imaging Basics

It is important to have realistic expectations for what ocular imaging in glaucoma can provide, as disappointment occurs when expectations exceed reality. CSLO, SLP, and OCT cannot diagnose glaucoma, nor can they diagnose glaucomatous progression. They can be used, however, to create the foundation on which to build these diagnoses. These technologies produce objective, quantitative, accurate, and precise measurements of ONH features, the retinal nerve fiber layer (RNFL), and macular substructure.

Reproducibility of Measures and Statistical Image Analysis

Reproducibility is high with each of the technologies mentioned,[10–14] and commercially available software can be used with each to measure change over time.[15–19] This is a major step forward, as previous iterations of these technologies did not include progression detection software, and earlier still, there was no normative database with which to compare the patient at hand. The devices can each statistically determine whether the structural features of the ONH and RNFL of a given individual fall within or outside the normal range and whether statistically significant change has occurred over time.

Technology Primer

CSLO takes a series of images of coronal planes that vary in tissue depth. The images are then combined and the surface topography of the tissue mapped. Depth information is present, but axial resolution is limited to approximately 300 μm. The ability to discriminate between glaucomatous and healthy eyes is good,[20] and the algorithm for detection of change over time has been validated in clinical studies. More change events are seen using CSLO than perimetry.[15]

SLP uses polarized light shone into the eye and reflected by structures in the eye back to a detector to determine the

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amount of birefringent tissue in the light path. Multiple ocular structures are birefringent, but only the RNFL is of interest in the case of SLP for glaucoma. An SLP scan of the macula, which has no RNFL in the foveola, is used as a baseline to assess non-RNFL ocular birefringence in a given individual. The peripapillary area is then scanned and RNFL assessed. The current commercially available SLP configuration has good glaucoma-discriminating ability, and its glaucoma progression algorithm has been evaluated in clinical studies.[21–23]

OCT is interferometry used to measure distances between interfaces. An OCT cross-sectional image, a B-scan, is made up of multiple single-axial scans (A-scans). A data set of multiple B-scans creating a 3D OCT can be obtained with the current commercially available OCT, which acquires approximately 25,000 to 55,000 A-scans per second. The 3D OCT can then be analyzed arbitrarily post hoc and thicknesses of various retinal substructures measured. In glaucoma assessment, the circumpapillary RNFL continues to be the strongest discriminator of glaucoma status, although excellent differentiation of glaucomatous and healthy eyes may be performed through the evaluation of ONH parameters or macular layers.[24–26] In the macula, the inner retina is most affected by glaucomatous damage, and measurements of the macular RNFL, ganglion cell layer, and inner plexiform layer produce a glaucoma-discriminating ability similar to the circumpapillary RNFL.[27,28] A clinical study evaluating RNFL thickness over time in glaucomatous eyes showed detection of more change-indicating events by OCT than were shown by perimetry.[19] Further, when RNFL thickness change is compared in glaucomatous eyes defined as progressing by perimetry or ONH photographs, the rate of change in progressing eyes is greater than that in nonprogressing eyes.[29,30]

Predicting the Development of Glaucoma

CSLO, SLP, and OCT each show differences consistent with glaucoma in ocular hypertensive eyes that go on to develop glaucoma or in glaucomatous eyes that progress.[21,31–33] An eye with a thinner RNFL or neuroretinal rim at baseline, for example, is more likely to develop glaucoma in an individual with ocular hypertension or progress in the presence of glaucoma.

The Venn Diagram Problem

A great problem in the evaluation of glaucoma progression is the lack of a gold standard. It is not clear which technology best defines glaucoma progression. Given a cohort of subjects, different technologies will define different eyes as progressing. Not only will structure and function be identified as occurring in different eyes, but even structure measured with different devices will show progression in different eyes in the same cohort.[29] This lack of overlap among eyes showing change is commonly referred to as the Venn diagram problem.

Summary

The major advantage of ocular imaging in glaucoma is that it is reproducible and provides an accurate, objective, quantitative assessment of the status of the ocular structure. This technology is useful for the diagnosis of glaucoma and the detection of progression and for identifying eyes at high risk of conversion to or progression of glaucoma. Ocular imaging reduces uncertainty and repeated perimetric testing, especially in cases of structure–function correspondence; however, progression identified by one technology is often not mirrored by others. This area requires additional investigation to determine the root of the Venn diagram problem.

Can We Detect Early Signs of Ganglion Cell Degeneration before Cell Death?

Retinal ganglion cells have axons, cell bodies, and dendrites. The axons form the RNFL, the cell bodies form the retinal ganglion cell layer, and the dendrites synapse in the inner plexiform layer. There is some evidence of changes in the inner plexiform layer as an early sign of glaucomatous damage, perhaps indicating retraction of dendrites. In addition, the RNFL may thin without actual cell death, as evidenced by thickening of the RNFL after surgical IOP reduction.[34,35]

In glaucomatous children, there is clearly a detectable and often dramatic change in the ONH, with shrinkage of the ONH cup after filtration surgery.

There is a suggestion that SLP may detect changes in birefringence before change in RNFL thickness or in ONH function.[36] These differences may reflect alterations in axonal mitochondria, microtubules, or other intracellular elements or organelles.

How Does This Translate into Better Treatment?

Ocular Imaging Brings the Clinician to the Level of an Expert Observer

Whether a patient is seen by a glaucoma specialist or a comprehensivist, clinical interpretation of the ONH is subjective and variable. Ocular imaging produces ONH, RNFL, and macular measurements at least as good as those of an expert observer.[37,38] Although imaging technology requires interpretation and the quality and algorithm performance must be checked, it has the potential to bring the clinician to the level of an expert observer.

Early Detection Enables Early Treatment

Since ocular imaging can provide a high degree of certainty regarding glaucoma diagnosis and glaucoma progression, it is now feasible for the clinician to treat earlier than previously possible.[39] Early treatment reduces the functional impact of glaucoma and has the potential to decrease the incidence of blindness worldwide.

A Damaged ONH Needs More Intensive Treatment

Chandler and Grant[40] said that a nerve damaged by pressure requires a lower pressure to prevent further damage. The corollary is that if glaucomatous damage is caught early, less intensive treatment may be adequate to control the disease and halt or slow progression. Ocular imaging allows identification of glaucoma and its progression earlier and with more certainty than would otherwise be possible, increasing the likelihood that the patient can be treated less intensively along the course of the disease, thus preserving vision and reducing the risk of blindness.

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