AMERICAN ACADEMY OF OPHTHALMOLOGY®

The Future of Imaging in Detecting Glaucoma Progression

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Ocular imaging has been heavily incorporated into glaucoma management and provides important information that aids in the detection of disease progression. Longitudinal studies have shown that the circumpapillary retinal nerve fiber layer is an important parameter for glaucoma progression detection, whereas other studies have demonstrated that macular parameters, such as the ganglion cell inner plexiform layer and optic nerve head parameters, also are useful for progression detection. The introduction of novel technologies with faster scan speeds, wider scanning fields, higher resolution, and improved tissue penetration has enabled the precise quantification of additional key ocular structures, such as the individual retinal layers, optic nerve head, choroid, and lamina cribrosa. Furthermore, extracting functional information from scans such as blood flow rate and oxygen consumption provides new perspectives on the disease and its progression. These novel methods promise improved detection of glaucoma progression and better insight into the mechanisms of progression that will lead to better targeted treatment options to prevent visual damage and blindness. *Ophthalmology 2017;124:S76-S82 © 2017 by the American Academy of Ophthalmology*

Glaucoma is a multifactorial optic neuropathy characterized by structural damage of retinal ganglion cells (RGCs) and their axons that is associated with vision loss and may lead to irreversible blindness.[1] Because glaucomatous damage is irreversible and effective treatment is available to halt further damage, glaucoma management should be optimized with precise micrometer-scale quantifications of ocular structures that improve detection of the disease and its progression.[2–4] The introduction of OCT technology more than 20 years ago provided in vivo detailed visualization of the optic nerve head (ONH) and retina and enabled the quantitative evaluation of these structures.[5,6] Circumpapillary retinal nerve fiber layer (RNFL) thickness is a common OCT measurement that provides comprehensive evaluation of all RGCs in an eye as they converge into the ONH.[2] When measured with spectral-domain OCT, the RNFL has been shown to differentiate between healthy and glaucomatous eyes.[7] The steady evolution of OCT technology has led to imaging with better resolution, higher scanning speeds, and advanced imaging patterns that has improved the reliability of OCT measurements and allowed for detection of minute changes that can improve the sensitivity of progression detection.

Assessment of glaucoma progression usually is based on event or trend analysis. Event-based progression determines when a measurement exceeds a pre-established threshold for change from baseline. Trend-based analysis quantifies the rate of a parameter's progression over time.[2,8] Conventionally, structural progression has been assessed using RNFL measurements; however, longitudinal studies have shown that other parameters, including the macular ganglion cell complex, ganglion cell-inner plexiform layer, and ONH parameters (rim area, cup area, and cup-to-disc ratio), also are useful for evaluating glaucoma progression.[9–11]

Despite the usefulness of OCT, there are also challenges in glaucoma detection and its progression with this technology. These challenges are the result of structural variability in healthy eyes, overlap in structural measurements between healthy and early glaucomatous eyes, and abnormal-appearing eyes that do not show any evidence of disease progression over time (e.g., physiologic cupping). Additionally, normal age-related structural loss can confound the interpretation of longitudinal glaucoma assessment.[12–15]

OCT comparison with functional visual testing, such as standard automated perimetry (SAP), also introduces a substantial challenge when assessing disease progression. The measurement variability of SAP is high and can be influenced by many confounding factors.[16,17] Additionally, the association between structural and functional abnormalities in glaucoma varies with disease severity, which also should be considered when assessing progression with these methods. In early stages of the disease, the high variability in SAP measurements often delays the possibility of detecting functional progression at a time when changes may be noted with structural assessment. A so-called tipping point was reported, illustrating the point in disease severity before which structural and functional changes often disagree and after which there is a strong association between the two.[18] Other studies have demonstrated that the SAP 24-2 testing strategy misses more central points compared with the 10-2 strategy in early glaucomatous losses.[19] Given the improved ability to detect macular thinning of RNFL and ganglion cell layer in recent iterations of the technology, an improved agreement between macular structure and visual function may be present in earlier stages than previously described.

Statement of Potential Conflict of Interest and Funding/Support: See page S82.

https://doi.org/10.1016/j.ophtha.2017.10.011
ISSN 0161-6420/17

In advanced disease, the opposite situation occurs in which assessment of the RNFL, as measured with OCT, is less sensitive than SAP in detecting progression after a minimum measurable thickness is reached; this is referred to as the *floor effect*.[20,21] It should be noted, however, that there are also limitations in visual field diagnosis of progression when mean sensitivities are between 19 and 15 dB and below because of a reduction in the asymptotic maximum response.[22,23] Furthermore, longitudinal analysis of OCT macular and ONH parameters have demonstrated their ability to detect structural progression even at stages where the peripapillary RNFL reached the floor effect thickness.[24] In a cohort of advanced glaucoma, defined by visual field mean deviation of ≤-21 dB, another study showed a significant rate of ganglion cell-inner plexiform layer thinning in 31% of the eyes.[25] It also has been demonstrated in a group of patients with advanced glaucoma that the ganglion cell-inner plexiform layer had a rate of change of -0.21 μm/year and that the dynamic range above the measurable floor was larger than the peripapillary RNFL and minimum rim width.[26] Therefore, macular OCT measurements provide an alternative for objective and quantitative monitoring of patients with advanced glaucoma.

To address these challenges and to explore opportunities in glaucoma progression detection, several new technologies, methods, and image processing tools are being studied. The assessment of the structure-function association with newer software and the introduction of advanced statistical methods to analyze and predict progression from large longitudinal data sets are promising tools to be incorporated into clinical practice. Additionally, novel methods and technologies are enabling the introduction of new biomarkers that may enhance the assessment of glaucoma progression further and may improve the understanding of the disease pathophysiologic features.

Novel OCT Technologies and Applications

Swept-Source OCT

Swept-source OCT is a newer generation of OCT that uses a short-cavity swept laser with a tunable wavelength of operation. It has a longer central wavelength (1050 nm) compared with conventional spectral-domain OCT (840 nm), providing deeper penetration and eliminating the depth-dependent signal drop-off observed with earlier generations of OCT. These capabilities enable imaging of deeper ocular structures, such as the choroid and lamina cribrosa (LC).[27–29] Additionally, improved visualization of the RGC layer allowed for the introduction of a model to estimate RGC quantity, which may be useful for understanding the longitudinal structure-function association.[30]

OCT Angiography

OCT angiography uses decorrelation motion contrast between rapidly repeated OCT cross-section scans to document retinal vessels. This is achieved by detecting variations in the intensity, phase properties, or both of the OCT signal resulting from the movement of red blood cells.[31] OCT angiography allows the peripapillary, ONH, and macular vasculature to be evaluated at various depths, exposing several vascular networks.[32–34] The peripapillary and ONH capillaries have been demonstrated to be associated with glaucoma.[35–37] The flow index (mean decorrelation value on the en face retinogram) and vessel density (area occupied by large vessels and microvasculature) have been shown to be associated with disease severity as reflected by SAP global indices.[38] Additional studies demonstrated a reduction in peripapillary vessel density in the hemispheres corresponding to hemifield defects in visual fields.[39,40] In eyes with glaucoma and a single-hemifield defect, diminished vascular density of the macular and peripapillary regions also was demonstrated in unaffected hemifields.[41] OCT angiography of eyes with glaucoma and LC defects portrayed diminished vascular density corresponding to the locations of these defects.[42]

A recent longitudinal study with a short follow-up period of less than 14 months showed a significantly faster rate of change of the superficial capillary plexus density in glaucomatous eyes compared with glaucoma suspects and healthy eyes.[43] This promising initial result should be corroborated by additional studies evaluating changes in other regions.

Doppler OCT

Color Doppler imaging shows significantly lower blood flow velocities and higher resistive indexes in the central retinal artery, short posterior ciliary arteries, and ophthalmic artery in patients with clinically worsening primary open-angle glaucoma (POAG).[44,45] Doppler OCT previously was reported to measure total flow around the ONH, but small vessel flow could not be detected.[46] Recently, high-speed en face Doppler OCT showed reduced total retinal blood flow in diabetic eyes compared with healthy eyes.[47] The value of vascular flow quantification in assessing glaucoma progression is yet to be determined.

Adaptive Optics

The incorporation of adaptive optics (AO) systems into ophthalmic imaging has improved achievable image quality further.[48] AO corrects for the monochromatic optical aberrations of the eye, thus improving the resolution of ocular imaging technologies.[49] For example, AO OCT improves transverse resolution from the typical 20 μm to approximately 5 μm.[50] Pruning of RGC dendrites has been shown to be an early indicator of glaucomatous damage[51]; using an AO system conjugated with scanning laser ophthalmoscopy, investigators showed that imaging of individual RGC bodies is possible in humans.[52] Additional studies with AO systems have demonstrated changes in the LC microstructure in glaucomatous eyes.[53,54] Others have allowed detection of damage down to individual retinal fiber layer bundles and the inner and outer retinal layers in glaucoma.[55,56] However, this technology still presents some barriers to its widespread adoption, namely high cost, limited field of view, narrow depth of focus, and extended acquisition time.[48]