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Review article

Detecting optic nerve head deformation and retinal nerve fiber layer thinning in glaucoma progression

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ABSTRACT

The application of digital imaging technologies including confocal scanning laser ophthalmoscopy (CSLO), optical coherence tomography (OCT), and scanning laser polarimetry (SLP) has significantly improved the detection of optic nerve head (ONH) deformation and progressive retinal nerve fiber layer (RNFL) thinning for assessment of glaucoma progression. Algorithms for change analysis such as topographic change analysis and guided progression analysis perform event analysis of serial ONH surface height topology maps and RNFL thickness/RNFL retardance maps, respectively, providing a topographical display of the location of significant change. With spectral-domain OCT, it is feasible to delineate and measure the lamina cribrosa surface depth in addition to ONH surface depth and RNFL thickness. Growing evidence from experimental and clinical studies indicates that ONH and lamina cribrosa deformation can be observed prior to detectable RNFL thinning and functional loss in glaucoma. These findings lend support to the notion that upon detection of ONH/lamina cribrosa deformation, a time window for therapeutic intervention for better outcomes may exist. The ONH and the lamina cribrosa are therefore important targets for monitoring glaucoma progression. This review summarizes the latest findings comparing the performance of OCT, CSLO, and SLP for detection of progressive ONH and RNFL damages in glaucoma patients and the clinical implication and limitations of studying the morphological alteration of the ONH, lamina cribrosa, and RNFL in the assessment of glaucoma progression.

1. Introduction

Glaucoma is the most common form of chronic, progressive optic neuropathy. A previous report indicates that the number of people with glaucoma would increase to 79.6 million by 2020.[1] Early detection of optic nerve damage in glaucoma is pertinent to formulation of treatment plan to prevent or slow down irreversible loss of vision. Although all forms of optic neuropathies demonstrate loss of retinal ganglion cells and thinning of the retinal nerve fiber layer (RNFL), glaucoma is unique in exhibiting progressive deformation of the optic nerve head (ONH). Growing evidence suggests that ONH deformation occurs prior to RNFL and functional loss in glaucoma.[2–7] Deformation of the ONH and lamina cribrosa surfaces has been consistently demonstrated in nonhuman primates induced with experimental glaucoma by laser photocoagulation of the trabecular meshwork.[2–5,8–11] Proposed to be the primary site of optic nerve damage in glaucoma,[12] the lamina cribrosa represents a strategic location for early detection of disease deterioration behavior. Progressive deformation of the lamina cribrosa may represent an early biomarker for glaucoma development and progression. This review summarizes the digital imaging technologies and algorithms available in the clinic for evaluation of progressive ONH and RNFL changes, experimental and clinical studies that investigated ONH deformation and RNFL thinning in glaucoma progression, and the implication of detection of structural changes of the ONH in the management of glaucoma.

2. Imaging technologies for evaluation of ONH deformation and RNFL thinning

2.1. Confocal scanning laser ophthalmoscopy

Confocal scanning laser ophthalmoscopy (CSLO) is the most long-standing digital imaging instrument for evaluation of the ONH

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surface topology. The Heidelberg Retinal Tomograph 3 (HRT 3; Heidelberg Engineering, Heidelberg, Germany) is the latest commercially available model of CSLO. It constructs three-dimensional surface topographic image consisting of up to 384 pixels × 384 pixels × 64 pixels from multiple focal images captured axially along the ONH. Because CSLO does not collect any data below the retinal and ONH surfaces, it can only be used to monitor ONH surface deformation but not lamina cribrosa deformation nor RNFL thinning. Measurement of the neuroretinal rim area is feasible with HRT but the measurement is dictated by an arbitrary reference plane, which is defined 50 μm posterior to the mean retinal height between 350° and 356° along a manually drawn contour line along the clinically visible optic disk margin. The topographic change analysis (TCA; Heidelberg Engineering), developed by Chauhan and colleagues,[13] is a well-established algorithm for measurement of progressive ONH surface height change in glaucoma patients. The TCA analyzes serial ONH topography images at a resolution of 96 superpixels × 96 superpixels (1 superpixel = 4 × 4 pixels). Individual superpixel ONH surface height measurements obtained in the baseline and follow-up visits are compared with the within-subject measurement variability. Superpixels with significant ONH surface depression and elevation are encoded in red and green, respectively, in the significance map, which is a topographical display of the location and the magnitude of ONH surface deformation (the saturation of the color increases with the degree of change; Fig. 1D). However, there is no consensus regarding the area and the depth of ONH surface height change that should be considered as clinically relevant. It is worth noting that ONH surface depression measured by the HRT may indicate the presence of ONH surface deformation, lamina cribrosa deformation, loss of the prelaminar tissue, or a combination of all these. HRT is not capable of delineating the individual components of the ONH changes.

2.2. Spectral-domain optical coherence tomography

2.2.1. Analysis of progressive RNFL thinning

Spectral-domain optical coherence tomography (SD-OCT) has gained popularity over the CSLO because of its higher scan speed, higher image resolution, and being able to quantify both the RNFL and ONH parameters. Whereas all the commercially available SD-OCT instruments have a scan speed >20,000 A-scans/second and an axial resolution of ~5 μm, the Cirrus high-definition OCT (HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA) is unique in having the most mature technology for detection of progressive RNFL thinning. The RNFL is conventionally imaged and measured using a circumpapillary scan with a diameter of approximately 3.45 mm. The Cirrus HD-OCT measures the RNFL thicknesses in an area of 6 × 6 mm^2, comprising 200 pixels × 200 pixels, displays the distribution of the RNFL in the RNFL thickness map, and reveals locations of RNFL abnormalities in the RNFL thickness deviation map.[14] For progression analysis, the guided progression analysis (GPA; Carl Zeiss Meditec) computes the differences of RNFL thickness measurements in serial RNFL thickness maps and reports the location of significant change in the RNFL thickness change map (Fig. 1B).[15] The GPA aligns and registers two baseline and the follow-up RNFL thickness maps, and compares the RNFL thickness differences of the individual superpixel (1 superpixel = 4 pixels × 4 pixels) locations between the baseline and the follow-up measurements with an estimate of test–retest variability. Superpixels are encoded in yellow in the OCT RNFL thickness change map if the RNFL thickness differences between the two baseline and follow-up examinations are greater than the test–retest variability. Superpixels are encoded in red if the change is confirmed in a consecutive visit. It has already been demonstrated that GPA of the RNFL thickness maps is useful to discern different patterns of progressive RNFL thinning including widening and deepening of RNFL defects.[15] Although GPA also provides a trend analysis of the average superior and inferior RNFL thicknesses, these analyses are limited to the circumpapillary RNFL measurement. Trend analysis of the RNFL thickness map has not yet been developed for routine clinical use.

2.2.2. Analysis of progressive ONH changes

Analysis of progressive deformation of the ONH surface and the laminar cribrosa surface is less straightforward with OCT as no image and statistical analysis package for detection of ONH and laminar cribrosa surface change has been incorporated into the existing OCT platforms. With enhanced depth imaging of the SPECTRALIS OCT (Heidelberg Engineering) and the swept-source OCT (e.g., the Atlantis OCT, Tokyo, Japan), clear visualization of the anterior (and sometimes posterior) laminar cribrosa surface and reliable estimation of the lamina cribrosa surface depth have become possible. OCT B scans can be exported from the OCT instrument for measurement of lamina cribrosa surface depth and optic nerve head surface depth (ONHSD) using a customized developed computer program. Anterior lamina cribrosa surface depth (ALCSD) and ONHSD are most often measured with reference to the Bruch's membrane opening (BMO) in experimental and clinical studies measuring deep ONH changes in glaucoma.[2–5,9–11] The ALCSD represents the perpendicular distances from a line joining the BMO, the reference line, to the discernible anterior laminar surface, which can be identified as the intersection between the horizontal high-intensity signal below the disk surface and the high-intensity vertical striations (Fig. 2B).[2] The ONHSD represents the perpendicular distances from the reference line to the ONH surface (Fig. 2C). Because the scan locations are registered at the baseline, it is feasible to image the same locations in the follow-up visits and track the changes of the ONH structures. It is uncertain, however, what type (radial vs. raster scans) and how many B scans are required to reliably detect ONH and lamina cribrosa surface change. Localized changes would be missed if the B-scan sampling density is low. Although the BMO reference line/plane is a widely adopted standard for measurement of ALCSD and ONHSD, the long-term stability of the BMO reference line/plane remains unclear. Age-related choroidal thinning may lead to anterior displacement of the ONH and laminar surfaces, confounding change analysis of ALCSD and ONHSD in glaucoma progression.[16]

2.3. Scanning laser polarimetry

The scanning laser polarimetry (SLP) uses polarized light to measure the relative phase retardance of the RNFL. The GDx enhanced corneal compensation (ECC; Carl Zeiss Meditec) is the latest generation of SLP. It introduces a known bias retarder, which then is removed mathematically to compensate for the retardance signal induced by the crystalline lens and the cornea. The GDx ECC uses the same GPA as that in the Cirrus HD-OCT for detection of progressive loss of RNFL retardance (Fig. 3). Although it has been shown that loss of RNFL retardance detected by SLP preceded RNFL thinning detected by OCT in nonhuman primates induced with experimental glaucoma,[3,17] a prospective clinical study demonstrated otherwise. Following 116 glaucoma patients for an average of 55 months with GDx ECC measurement of RNFL retardance and Cirrus HD-OCT measurement of RNFL thickness at 4-month intervals, we observed that progressive RNFL thinning was detected more frequently than progressive reduction of RNFL retardance at a similar level of specificity (14.6% and 4.3% of eyes showed progressive reduction of RNFL thickness and RNFL retardance, respectively).[18] For eyes with loss of RNFL thickness and RNFL