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Optic Nerve Head Deformation in Glaucoma

The Temporal Relationship between Optic Nerve Head Surface Depression and Retinal Nerve Fiber Layer Thinning

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Objective: To investigate the temporal relationship between optic nerve head (ONH) surface depression and retinal nerve fiber layer (RNFL) thinning measured by confocal scanning laser ophthalmoscopy (CSLO) and spectral-domain optical coherence tomography (SD-OCT), respectively, during the course of glaucoma progression.

Design: Prospective, longitudinal study.

Participants: A total of 146 eyes of 90 patients with glaucoma and 70 normal eyes of 35 healthy individuals followed for an average of 5.4 years (range, 48.0–76.6 months).

Methods: Eyes were imaged by CSLO (Heidelberg Retinal Tomograph [HRT]; Heidelberg Engineering, GmbH, Dossenheim, Germany) and SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec AG, Dublin, CA) at approximately 4-month intervals for measurement of ONH surface topography and RNFL thickness, respectively. Significant ONH surface depression and RNFL thinning were defined with reference to Topographic Change Analysis (TCA) with HRT and Guided Progression Analysis (GPA) with Cirrus HD-OCT, respectively. The survival probabilities were compared with a Cox proportional hazards model.

Main Outcome Measures: Number of eyes with progressive ONH and RNFL changes and the sequence of changes.

Results: A total of 3238 OCT and 3238 CSLO images obtained in the same follow-up visits were analyzed. At a specificity of 94.3% (4 eyes showed ONH surface depression and 4 eyes showed RNFL thinning in the normal group), 57 eyes (39.0%) had ONH surface depression, 46 eyes (31.5%) had RNFL thinning, and 23 eyes (15.8%) had evidence of both in the glaucoma group. Among these 23 eyes, 19 (82.6%) had ONH surface depression detected before RNFL thinning, with a median lag time of 15.8 months (range, 4.0–40.8 months). Although only 7.0% of eyes (4/57) had RNFL thinning at the onset of ONH surface depression, 45.7% (21/46) had ONH surface depression at the onset of RNFL thinning. The survival probability of eyes with ONH surface depression was significantly worse than eyes with RNFL thinning ($P = 0.002$).

Conclusions: With reference to the HRT TCA and OCT GPA, ONH surface depression occurred before RNFL thinning in a significant proportion of patients with glaucoma. A time window for therapeutic intervention may exist on detection of ONH surface depression before there is observable RNFL thinning in glaucoma. *Ophthalmology 2014;■:1–9 © 2014 by the American Academy of Ophthalmology.*

Although all forms of optic neuropathies exhibit loss of retinal ganglion cells and their axons, glaucoma is unique in having both retinal ganglion cell degeneration and chronic progressive deformation and remodeling of the optic nerve head (ONH). Characteristic features of ONH changes in glaucoma include narrowing of the neuroretinal rim, excavation of the optic cup, loss of prelaminar neural tissue, and deformation of the lamina cribrosa. Quantifying both ONH deformation and retinal nerve fiber layer (RNFL) thinning, a surrogate of loss of retinal ganglion cell axons is relevant to evaluate glaucoma progression. With the advent of digital imaging technologies, reproducible measurements of the ONH and RNFL thickness become feasible.[1–8] Confocal scanning laser ophthalmoscopy (CSLO) quantifies the surface topography of the ONH, whereas optical coherence tomography (OCT) is most widely used to measure the RNFL thickness. Although both CSLO and OCT are capable of detecting longitudinal changes of the ONH and RNFL, respectively, the sequence of change in glaucoma progression remains obscure. Specifically, it is unclear whether the topographic changes of the ONH are a cause or a consequence of RNFL thinning. Furthermore, there is no consensus regarding whether ONH topography or RNFL thickness is better for tracking glaucoma progression. Investigating the sequence of ONH and RNFL changes is thus not only relevant to understanding the role of ONH remodeling and deformation in glaucomatous optic nerve damage but also pertinent in devising optimal strategies for detection of disease progression.

Experimental glaucoma studies in nonhuman primates have provided valuable insights into the sequence of ONH and RNFL changes in glaucoma.[9–12] The studies by Fortune

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et al[9,10] and Strouthidis et al[11] suggested that ONH surface height changes measured by CSLO occurred before reduction of RNFL thickness measured by OCT. However, the relatively short follow-up duration (in months rather than in years) and nonphysiologic intraocular pressure (IOP) fluctuation after laser photocoagulation of the trabecular meshwork (with peak IOP up to 50−60 mmHg[9−11]) may limit the generalizability of the studies to human glaucoma. In the current study, we compared the performance of CSLO and OCT for detection of ONH and RNFL changes and investigated whether ONH surface depression developed before RNFL thinning during the course of glaucoma progression.

Methods

Subjects

A total of 125 subjects, including 90 patients with glaucoma and 35 normal healthy individuals, were consecutively enrolled and followed during the period from June 2007 to November 2013 at the University Eye Center, the Chinese University of Hong Kong. All subjects underwent a full ophthalmic examination, including measurement of visual acuity, refraction and IOP, gonioscopy, and fundus examination. The optic disc was examined with slit-lamp biomicroscopy, and color optic disc stereophotographs were captured. Eyes were included if the visual acuity was at least 20/40 and excluded if there was macular disease, refractive or retinal surgery, or neurologic disease. No subjects had diabetes mellitus. Patients with glaucoma were identified on the basis of the presence of visual field defects (described later) with corresponding optic disc and RNFL changes in at least 1 eye independent of the level of IOP. During the follow-up, patients were treated at the discretion of the attending ophthalmologists with reference to the target IOP. Fourteen eyes (9.6%) had trabeculectomy, and 116 eyes (79.5%) were on at least 1 glaucoma medication at the latest follow-up visit. Normal individuals had no structural optic disc abnormalities and no RNFL defects, no history of IOP >21 mmHg, no visual field defect, and no history of ocular disease, neurologic disease, or major systemic illness. Both eyes had OCT RNFL imaging (Cirrus HD-OCT; Carl Zeiss Meditec AG, Dublin, CA), CSLO optic disc imaging (Heidelberg Retinal Tomograph [HRT]; Heidelberg Engineering, GmbH, Dossenheim, Germany), and visual field testing (Humphrey Field Analyzer II-I; Carl Zeiss Meditec AG) in the same visit at approximately 4-month intervals for at least 48 months. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and approved by local research ethics committee with written informed consent obtained.

Optical Coherence Tomography Retinal Nerve Fiber Layer Imaging

The details of the principles of spectral-domain OCT have been described,[13] and the methods of OCT RNFL imaging have been described in our earlier studies.[1,14] The acquisition rate of the Cirrus HD-OCT was 27 000 A-scans per second, and the transverse and axial resolutions were 15 μm and 5 μm, respectively. An "optic disc cube" scan protocol was used to measure the RNFL thickness in a 6×6 mm^2 region (200×200 pixels) centered at the optic disc, and an RNFL thickness map was generated. Only images with signal strength ≥7 were included in the analysis. Saccadic eye movement was detected with the line-scanning ophthalmoscope overlaid with OCT en face images. Images with motion artifact, poor centration, poor focus or missing data were detected by the operator at the time of imaging, and re-scanning was performed in the same visit.[1,14]

Detection of Progressive Retinal Nerve Fiber Layer Thinning

The Cirrus HD-OCT Guided Progression Analysis (GPA) (Carl Zeiss Meditec AG) was used to analyze serial RNFL thickness maps (200×200 pixels) for detection of progressive RNFL thinning.[15] Guided Progression Analysis automatically aligned and registered 2 baseline and the follow-up OCT images so that the same superpixel (1 superpixel = 4×4 pixels) locations could be analyzed for detection of change. The difference in RNFL measurement of an individual superpixel between the baseline and the follow-up RNFL thickness maps was compared with an estimate of test−retest variability of that particular superpixel (proprietary database from Carl Zeiss Meditec AG). Superpixels with an RNFL measurement difference exceeding the test−retest variability between a follow-up and the first and second baseline images would be encoded in yellow in the OCT RNFL thickness change map (50×50 superpixels). If the same changes were evident in an additional consecutive follow-up image, the superpixels would be encoded in red. In this study, the 2 baseline images were separated by approximately 4 months and progressive RNFL thinning was confirmed when an area of more than 20 superpixels (factory default) was encoded in red in the RNFL thickness change map for at least 2 consecutive visits. At least 3 consecutive follow-up visits showing significant RNFL thickness reduction were required to confirm progressive RNFL thinning.

Confocal Scanning Laser Ophthalmoscopy of the Optic Nerve Head

Optic disc imaging was performed with the HRT 3 (Heidelberg Engineering). A 3-dimensional topographic image consisting of up to 384×384×64 pixels was constructed from multiple focal planes axially along the ONH. An average of 3 consecutive scans was obtained and aligned to compose a single mean topography for analysis. The optic disc margin was outlined by an experienced examiner on the mean topographic image. Once the contour line was drawn, the software automatically calculated all the optic disc measurements. The area above the reference plane was defined as the rim, and the area below was defined as the cup. The reference plane was defined at 50 μm posterior to the mean retinal height between 350° and 356° along the contour line. Re-scanning was performed in the same visit if motion artifacts were detected immediately after the imaging. All eyes included in the analysis had an image quality standard deviation ≤30 μm.

Detection of Progressive Optic Nerve Head Surface Depression

The HRT Topographic Change Analysis (TCA, Heidelberg Engineering) was used to analyze serial ONH topography images (96×96 superpixels; 1 superpixel = 4×4 pixels) for detection of ONH surface depression.[16] Individual superpixel ONH surface height measurements were compared between the baseline and each of the follow-up examinations with an F test. The pooled variability of the baseline and the follow-up examinations of a particular pixel was compared with the within variability of the baseline and the follow-up examinations (with an error probability of the F-test <5%). If significant ONH surface depression was detected in a superpixel and confirmed with ≥2 consecutive follow-up visits, the superpixel would be encoded in red in the significance map. The saturation of the color increased with the magnitude of surface height change. Progressive ONH surface