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Ganglion Cell–Inner Plexiform Layer Change Detected by Optical Coherence Tomography Indicates Progression in Advanced Glaucoma

Joong Won Shin, MD,[1] *Kyung Rim Sung, MD, PhD,*[1] *Gary C. Lee, PhD,*[2] *Mary K. Durbin, PhD,*[2] *Daniel Cheng, OD*[2]

Purpose: To examine the performance of Guided Progression Analysis (GPA; Carl Zeiss Meditec, Dublin, CA) in spectral-domain optical coherence tomography (OCT) in detecting progressive thinning of ganglion cell–inner plexiform layer (GCIPL) and retinal nerve fiber layer (RNFL) in glaucoma.

Design: Longitudinal, observational study.

Participants: A total of 196 eyes of 123 primary open-angle glaucoma patients (mean follow-up, 5.0 years).

Methods: Macular GCIPL and peripapillary RNFL thicknesses were measured by Cirrus HD-OCT (Zeiss, Dublin, CA), and progressive GCIPL and RNFL thinning were assessed by GPA. The reference standard of glaucoma progression was determined by visual field (VF) progression. Glaucomatous eyes were classified into mild (117 eyes) or moderate to advanced (79 eyes) groups based on VF defects. Ganglion cell–inner plexiform layer and RNFL thinning rates were compared between progressors and nonprogressors. Visual field survival estimates in eyes with and without progressive GCIPL and RNFL thinning were evaluated by Kaplan–Meier survival analysis and compared with the log-rank test.

Main Outcome Measures: Progressive GCIPL and RNFL thinning assessed by OCT GPA.

Results: Seventy-six eyes (38.8%) and 43 eyes (21.9%) demonstrated progressive GCIPL and RNFL thinning, respectively, and 48 eyes (24.5%) were classified as progressors by reference standard. The rate of change in the average GCIPL thickness was significantly higher in progressors (-1.05 ± 0.98 μm/year for mild glaucoma and -0.66 ± 0.30 μm/year for moderate to advanced glaucoma) than in nonprogressors (-0.47 ± 0.54 μm/year for mild glaucoma and -0.31 ± 0.50 μm/year for moderate to advanced glaucoma), regardless of glaucoma severity ($P < 0.05$). Eyes with progressive GCIPL thinning had lower VF survival estimates than eyes without, regardless of glaucoma severity. However, the rate of change in the average RNFL thickness did not differ significantly in moderate to advanced glaucoma ($P = 0.765$; -0.26 ± 0.55 μm/year for progressors and -0.33 ± 0.92 μm/year for nonprogressors), and VF survival estimates did not differ significantly between eyes with and without progressive RNFL thinning in moderate to advanced glaucoma ($P = 0.781$).

Conclusions: Ganglion cell–inner plexiform layer GPA provides a new approach for evaluating glaucoma progression. It may be more useful for detecting progression in the advanced stages of glaucoma than RNFL GPA. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

Glaucoma is a progressive optic neuropathy accompanied by characteristic structural changes and functional visual field (VF) loss. Because glaucoma can result in irreversible loss of visual function, detecting progression is an important issue in monitoring glaucoma patients. Visual field assessment has been used as a primary outcome to determine glaucoma progression in many landmark glaucoma treatment trials.[1–3] However, progressive loss of the retinal ganglion cells and their axonal fibers can occur before VF decay becomes detectable.[4–6] Optical coherence tomography (OCT) is a reliable method to detect glaucoma and has been used widely for the quantitative structural evaluation of parameters such as the thickness of the peripapillary retinal nerve fiber layer (RNFL) and the macular ganglion cell–inner plexiform layer (GCIPL).[7–9] Progressive change in RNFL thickness can be identified objectively by serial analysis of OCT measurements and is predictive of VF progression.[10–12] Although glaucomatous damage involves not only the axons, but also the retinal ganglion cells, progressive changes in GCIPL thickness in glaucoma have not been examined comprehensively with OCT.

Macular GCIPL measurement may be a useful method for monitoring glaucomatous progression. It has excellent long-term intervisit reproducibility, which enhances reliability when comparing GCIPL thickness in progression monitoring.[13] In addition, GCIPL thickness is less likely to reach the measurement floor than RNFL thickness in advanced glaucoma, which suggests that GCIPL thickness is better for detecting progression.[14,15] Therefore, there is an increasing need to develop an effective tool for monitoring the progressive changes of GCIPL thickness.

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Published by Elsevier Inc.

http://dx.doi.org/10.1016/j.ophtha.2017.04.023
ISSN 0161-6420/17

A recent update of Guided Progression Analysis (GPA) of Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) provides longitudinal analysis of GCIPL progression. The Cirrus GPA can perform event analysis and trend analysis for GCIPL thickness. Event analysis evaluates the differences in GCIPL thickness between 2 baseline and follow-up images in a 6×6-mm^2 macular GCIPL thickness map. If the difference in a specific area is outside the range of the test–retest variability, then it is identified as progression in the GCIPL thickness change map with yellow or red codes. Linear regression is used to analyze the trend of the rate of change in GCIPL thickness over time. Following this change with GCIPL GPA, as well as RNFL GPA, may be an effective alternative in detecting glaucoma progression. Therefore, in this study, we investigated the performance of OCT GPA in detecting progressive GCIPL and RNFL thinning and in predicting VF progression.

Methods

Participants

We retrospectively recruited 123 patients with primary open-angle glaucoma by reviewing medical records at the Glaucoma Clinic of the Asan Medical Center (Seoul, Korea) between April 2009 and December 2016. The institutional review board of the Asan Medical Center approved the present study, informed consent was waived owing to the retrospective nature of the study, and the study design was executed in accordance with the principles of the Declaration of Helsinki. At the initial evaluation, all participants underwent complete ophthalmologic examinations, including measurement of the best-corrected visual acuity, intraocular pressure by Goldmann applanation tonometry, and central corneal thickness with the DGH-550 device (DGH Technology, Exton, PA), as well as slit-lamp biomicroscopy and gonioscopy. They were followed up every 6 months for stereoscopic optic disc and red-free RNFL photography (AFC-210; Nidek, Aichi, Japan), GCIPL and RNFL imaging (Cirrus HD-OCT; Carl Zeiss Meditec), and VF testing (Humphrey Field Analyzer, Swedish interactive threshold algorithm 24-2; Carl Zeiss Meditec).

The inclusion criteria were best-corrected visual acuity of 20/30 or better and a normal anterior chamber and open angle on slit-lamp and gonioscopic examinations. At least 6 reliable VF and OCT examinations at separate visits were required. Glaucoma was diagnosed by the presence of RNFL defects or glaucomatous optic disc changes (neuroretinal rim thinning, disc excavation, or disc hemorrhage) and corresponding VF defects as confirmed by at least 2 reliable VF examinations. Only reliable VF test results (i.e., false-positive errors <15%, false-negative errors <15%, and fixation loss <20%) were included in the study. Glaucomatous VF defects were defined as a cluster of 3 or more nonedge contiguous points on a pattern deviation plot with a P value of less than 0.05 (with at least having a P value of less than 0.01) as confirmed by at least 2 consecutive examinations, a pattern standard deviation with a P value of less than 0.05, or glaucoma hemifield test results outside normal limits. Patients with any ophthalmic or neurologic disease known to affect the optic nerve head or VF were excluded. If surgical or laser treatment was performed during the study follow-up period, only data obtained in the period before the treatment were analyzed. At least 3 years of follow-up were needed for inclusion.

Optical Coherence Tomography Imaging

Spectral-domain OCT GCIPL and RNFL imaging were performed with the Cirrus HD-OCT macular and optic disc cube scans, respectively. The macular cube scan generated a GCIPL thickness map in a 6×6-mm^2 area (512×128 pixels) centered at the fovea. Macular GCIPL thickness was measured within an annulus with inner vertical and horizontal diameters of 1 and 1.2 mm, respectively, and outer vertical and horizontal diameters of 4 and 4.8 mm, respectively. The optic disc cube scan generated an RNFL thickness map in a 6×6-mm^2 area (200×200 pixels) centered at the optic disc. The circumpapillary RNFL thickness was measured in a circle of 3.46 mm in diameter. Only images with a signal strength of 7 or more were included. Images with motion artifacts, poor centering, or segmentation error were checked and discarded by the operator, with rescanning performed during the same visit.

Guided Progression Analysis of the Thickness of the Ganglion Cell–Inner Plexiform Layer and Retinal Nerve Fiber Layer

The Cirrus HD-OCT GPA (Carl Zeiss Meditec; software version 9.5) provides event and trend analysis for detecting progressive thinning of the macular GCIPL and peripapillary RNFL. Event analysis evaluates the differences in GCIPL or RNFL thickness between 2 baseline and follow-up examinations in a 6×6-mm^2 map (50×50 superpixels) and 3 summary GCIPL or RNFL parameters (average, superior, and inferior thicknesses). If the difference is confirmed to be outside the range of the test–retest variability, it is classified as "possible loss" with a yellow code in the GCIPL or RNFL thickness change map and the summary parameters, and it is classified as "likely loss" with a red code if the difference is evident and confirmed in a subsequent follow-up examination. At least 20 contiguous superpixels in the GCIPL or RNFL thickness change maps are required for a change to be classified as significant. Trend analysis evaluates the rate of change in the GCIPL and RNFL thicknesses (average, superior, or inferior) over time using linear regression. In the current study, progressive GCIPL or RNFL thinning was defined as when a likely loss in the event analysis was detected during the study follow-up and the same changes were observed in the latest follow-up visit.

Visual Field Progression

We adopted VF progression as the reference standard for glaucoma progression in the current study. The first VF test was excluded to minimize the learning effect. VF progression was determined by the Early Manifest Glaucoma Trial criteria or linear regression analysis of the VF index. Early Manifest Glaucoma Trial progression was confirmed when at least 3 test points were flagged as having deteriorated significantly at the same test point locations in 3 consecutive fields.[2] These changes also had to have been observed at the latest follow-up visit. In the linear regression analysis, VF progression was defined as a significant negative slope between VF index and age.

Statistical Analysis

Statistical analysis was performed using the statistical package R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS software version 20 (IBM Corp., Armonk, NY). The general estimating equation method was used to adjust for correlation between 2 eyes of the same patient.[16] Glaucomatous eyes were classified into mild (mean deviation

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