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Temporal Relation between Macular Ganglion Cell–Inner Plexiform Layer Loss and Peripapillary Retinal Nerve Fiber Layer Loss in Glaucoma

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Purpose: To investigate the temporal relationship between inferior macular ganglion cell–inner plexiform layer (mGCIPL) loss and corresponding peripapillary retinal nerve fiber layer (pRNFL) defect on the optical coherence tomography (OCT) deviation map in glaucoma.

Design: Retrospective, observational study.

Participants: A total of 151 patients with early-stage glaucoma (visual field [VF] mean deviation between −1.5 and −5.5 decibels [dB]).

Methods: Spectral-domain OCT mGCIPL and pRNFL deviation maps were obtained for the baseline (from January 2012 to August 2012) and again for the follow-up (from January 2015 to August 2015). An integrated deviation map thereafter was merged by vascular landmark–guided superimposition of mGCIPL and pRNFL deviation maps onto RNFL imagery. On the basis of an earlier schematic model, the inferotemporal peripapillary area was divided into (1) the macular vulnerability zone (MVZ) and (2) the inferoinferior portion.

Main Outcome Measures: Temporal sequence of inferior mGCIPL loss and corresponding pRNFL (i.e., pRNFL in MVZ) defect on integrated deviation map.

Results: At baseline, 99 (65.6%) of the 151 eyes showed inferior mGCIPL loss. In addition, 112 eyes (74.2%) and 5 eyes (3.3%) showed inferoinferior pRNFL defect and pRNFL defect in the MVZ, respectively. At the 3-year follow-up, 112 (74.2%) of the eyes showed inferior mGCIPL loss, whereas 123 eyes (81.5%) and 25 eyes (16.6%) showed inferoinferior pRNFL defect and pRNFL defect in the MVZ, respectively. Ninety-four eyes initially showed inferior mGCIPL loss without pRNFL defect in the MVZ; among them, 19 (20.2%) subsequently showed defect during the 3-year follow-up interval. Meanwhile, among the 52 eyes without preexisting inferior mGCIPL loss, only 1 (1.9%; $P < 0.001$) developed a pRNFL defect in the MVZ during the 3-year follow-up interval.

Conclusions: In eyes with early glaucoma, mGCIPL change is frequently detected before corresponding pRNFL change. This could be the result of a superior sensitivity of mGCIPL deviation map that allows detection of an abnormality in the mGCIPL thickness earlier. In this light, OCT pRNFL analysis alone likely would overlook macular damage. Macular OCT imaging should be included in the imaging algorithm for the serial observation of patients with glaucoma. *Ophthalmology 2017;124:1056-1064 © 2017 by the American Academy of Ophthalmology*

Progressive retinal ganglion cell (RGC) axonal thinning occurs in glaucoma.[1–5] Because RGC axonal thickness is greatest at the peripapillary retina,[6–8] conventional optical coherence tomography (OCT) scan has measured the peripapillary retinal nerve fiber layer (pRNFL) thickness for discrimination of glaucomatous structural loss. However, glaucoma involves not only the RGC axons but also the bodies and dendrites.[9–13] Therefore, assessment of all RGC components is vital to successful monitoring of glaucoma.

Mounting evidence in the investigation of glaucomatous damage implicates early macular involvement.[14–17] The utility of pRNFL thickness evaluation by frequency-domain OCT for detection of glaucomatous macular damage was investigated by Wang et al.[18] They reported that the temporal quadrant of disc cube scan criterion missed 47 (77%) of the 61 eyes showing abnormal thinning on macular scan. Thus, the typical analyses of the disc cube OCT scan using pRNFL thickness maps potentially overlook glaucomatous macular damage.

Our group further explored the relationship between abnormal inferior macular ganglion cell–inner plexiform layer (mGCIPL) thinning and corresponding pRNFL thinning on the OCT deviation map.[19] Of note, all cases of pRNFL defect in the macular vulnerability zone (MVZ)[12] *also showed* inferior mGCIPL loss. However, there were several cases of inferior mGCIPL loss that *did not show* pRNFL defect in the MVZ. This suggests that inferior mGCIPL change is detected statistically before pRNFL change in the MVZ. Furthermore, longitudinal investigation is obviously called for.

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This study scrutinized 3-year interval longitudinal data on the pattern of progression of inferior hemiretinal defect to confirm inferior macular damage's temporal relationship with corresponding pRNFL damage on the OCT deviation map.

Methods

This study, as approved by the Institutional Review Board of Seoul National University Hospital, adhered to the Declaration of Helsinki. The electronic medical records (compiled by author K.H.P. of the Glaucoma Clinic of Seoul National University Hospital) representing both the baseline (from January 2012 to August 2012) and the follow-up period (from January 2015 to August 2015) of patients with primary open-angle glaucoma (POAG) were retrospectively reviewed.

Study Subjects

All of the subjects underwent complete ophthalmologic examinations, including best-corrected visual acuity measurement, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, refractive error with an autorefractor (KR-890; Topcon Corporation, Tokyo, Japan), corneal pachymetry (Pocket II Pachymeter Echo graph; Quantel Medical, Clermont-Ferrand, France), slit-lamp biomicroscopy, gonioscopy, and dilated fundus examination. Upon maximal pupil dilation, the subjects underwent stereo optic disc photography, red-free retinal nerve fiber layer (RNFL) photography (Vx-10; Kowa Optimed Inc., Tokyo, Japan), and Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). They also underwent standard automated perimetry using the Swedish interactive threshold algorithm according to the 30-2 standard program (Humphrey Field Analyzer II; Carl Zeiss Meditec).

The included subjects all showed spherical refraction greater than −6 diopters (D) and less than 3 D, normal open anterior chamber angle, and reliable visual field (VF) tests (i.e., mean deviation [MD], −1.5 to −5.5 decibels [dB]). For minimization of inter-subject variability and false-positive error risk,[20] subjects showing an axial length (AL) shorter than 27.0 mm and an OCT computed disc area larger than 1.80 mm^2 were selectively enrolled. Only those showing an Image J software[21,22] measured fovea-to-disc angle between 3° and 9° were enrolled, to exclude eyes with extreme variation of the posterior pole.

Glaucomatous eyes were defined by the characteristic localized or diffuse neuroretinal rim thinning of the optic disc on stereo disc photography or by the presence of RNFL defect on red-free fundus imaging. Eyes with glaucomatous VF defect were defined as follows: (1) a 3-point cluster with a less than 5% probability in at least 1 pattern deviation map hemifield, at least 1 with a less than 1% probability or a 2-point cluster with a less than 1% probability; (2) outside normal limits glaucomatous hemifield test results; or (3) a pattern standard deviation more than 95% of the normal limits, as confirmed by at least 2 reliable examinations (false-positives/false-negatives <15%, fixation losses <15%).

Individuals identified for exclusion showed (1) a secondary cause of glaucomatous optic neuropathy, (2) a history of non-cataract intraocular surgery (including glaucoma filtering surgery) or retinal laser photocoagulation, and (3) a neurologic or systemic disease potentially affecting the retina or VF. In patients in whom both eyes were eligible, 1 eye was selected randomly.

Cirrus High-Definition Optical Coherence Tomography Measurement

The RNFL and ganglion cell−inner plexiform layer thickness measurements by Cirrus HD-OCT optic disc and macular scans, respectively, were carried out as described previously.[23] Subjects showing high-quality scans were included for further analysis. "High-quality" OCT images had a signal strength ≥8 (maximum = 10) and lacked any motion artifact, involuntary saccade, obvious decenteration misalignment, or algorithm segmentation failure. The deviation maps used were those obtained by Cirrus HD-OCT ganglion cell analysis or RNFL algorithms.

Integrated Deviation Map

An integrated deviation map was used for single fundus image evaluation of mGCIPL and pRNFL defects (Fig 1A and B). The map was created by mGCIPL and pRNFL deviation map superimposition onto RNFL photography as aligned by Photoshop software (Version 11.0; Adobe, San Jose, CA) based on vascular landmarks. The locations of inferotemporal pRNFL defect were categorized on the basis of the previous schematic model[12]: (1) the MVZ from the inferior temporal quadrant to the temporal inferior quadrant ("c" in Fig 1A) and (2) the inferoinferior portion ("b" in Fig 1A).

According to this schematic model, defects extending on each pRNFL deviation map 10 or more contiguous superpixel-sized wedge-shaped color (red) patterns across a 3.46-mm diameter calculation circle and 3 or more superpixels within that circle, were defined as abnormal.[24,25] In determining mGCIPL defect, on each mGCIPL deviation map, contiguous color-coded pixels of at least 10 superpixels in area and more than a boundary of 1 superpixel away from the inner annulus were detected.[23] The defect discrimination was performed independently by 2 masked experienced examiners (Y.K.K. and K.H.P.). Neither examiner was aware of the perimetric findings or any other clinical data (e.g., IOP).

Kappa Coefficients

The kappa coefficients for the assessment of defect presence or absence on the integrated deviation maps and those for the assessment of the location of pRNFL defects were calculated as a function of the interobserver agreement reliability.[26] The 2 graders showed excellent agreement on any evidence of inferior mGCIPL loss or pRNFL defect (kappa = 0.89; 95% confidence interval, 0.81−1.00; $P < 0.001$). They also showed good overall agreement in determining whether the pRNFL defect was presented in the MVZ or inferoinferior legion (kappa = 0.85; 95% confidence interval, 0.79−1.00; $P < 0.001$).

Data Analysis

A commercially available software package (SPSS for Windows, version 19.0, IBM-SPSS, Chicago, IL) was used for the statistical analyses. The proportions were compared by the chi-square test. The data in the current article are presented in the form of mean values with standard deviations. All of the P values, 2-sided, were considered significant at <0.05.

Results

A total of 162 POAG eyes, representing 162 patients, were initially included in the study. Eleven of them were excluded: 6 for a fovea-to-disc angle ≤3° or ≥9° or an AL longer than 27.0 mm; 3 for poor-quality stereo disc photography or RNFL photography; and 2 for nonmatching retinal vessel on the OCT deviation map and RNFL photography. The remaining 151 eyes of 151 patients were examined in the ensuing analysis (Fig 2). The subjects' demographic characteristics are summarized in Table 1. The