American Academy of Ophthalmology
The Eye M.D. Association

Diagnostic Classification of Macular Ganglion Cell and Retinal Nerve Fiber Layer Analysis

Differentiation of False-Positives from Glaucoma

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Purpose: To investigate the rate and associated factors of false-positive diagnostic classification of ganglion cell analysis (GCA) and retinal nerve fiber layer (RNFL) maps, and characteristic false-positive patterns on optical coherence tomography (OCT) deviation maps.

Design: Prospective, cross-sectional study.

Participants: A total of 104 healthy eyes of 104 normal participants.

Methods: All participants underwent peripapillary and macular spectral-domain (Cirrus-HD, Carl Zeiss Meditec Inc, Dublin, CA) OCT scans. False-positive diagnostic classification was defined as yellow or red color-coded areas for GCA and RNFL maps. Univariate and multivariate logistic regression analyses were used to determine associated factors. Eyes with abnormal OCT deviation maps were categorized on the basis of the shape and location of abnormal color-coded area. Differences in clinical characteristics among the subgroups were compared.

Main Outcome Measures: (1) The rate and associated factors of false-positive OCT maps; (2) patterns of false-positive, color-coded areas on the GCA deviation map and associated clinical characteristics.

Results: Of the 104 healthy eyes, 42 (40.4%) and 32 (30.8%) showed abnormal diagnostic classifications on any of the GCA and RNFL maps, respectively. Multivariate analysis revealed that false-positive GCA diagnostic classification was associated with longer axial length and larger fovea-disc angle, whereas longer axial length and smaller disc area were associated with abnormal RNFL maps. Eyes with abnormal GCA deviation map were categorized as group A (donut-shaped round area around the inner annulus), group B (island-like isolated area), and group C (diffuse, circular area with an irregular inner margin in either). The axial length showed a significant increasing trend from group A to C ($P = 0.001$), and likewise, the refractive error was more myopic in group C than in groups A ($P = 0.015$) and B ($P = 0.014$). Group C had thinner average ganglion cell–inner plexiform layer thickness compared with other groups (group A = B > C, $P = 0.004$).

Conclusions: Abnormal OCT diagnostic classification should be interpreted with caution, especially in eyes with long axial lengths, large fovea-disc angles, and small optic discs. Our findings suggest that the characteristic patterns of OCT deviation map can provide useful clues to distinguish glaucomatous changes from false-positive findings. *Ophthalmology 2014;■:1–9 © 2014 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Progressive loss of retinal ganglion cells and their axons is the key pathogenesis of glaucoma.[1] For several decades, the retinal nerve fiber layer (RNFL) has been the main focus of structural evaluation for detecting glaucoma. However, the main glaucomatous damage involves not only the axons but also the retinal ganglion cell bodies and dendrites. Therefore, assessment of the ganglion cell–inner plexiform layer (GCIPL) is of vital importance for the diagnosis of glaucoma.

Recent technologic advances in spectral-domain optical coherence tomography (SD-OCT) have facilitated the development of a ganglion cell analysis (GCA) algorithm that can automatically segment and measure macular GCIPL thickness in the macular region.[2,3] The great advantage of optical coherence tomography (OCT), besides providing actual GCIPL thickness measurements, is the generation of color-coded GCA maps that can present information on probable GCIPL defects as "outside normal limits" or "borderline" according to an internal normative database. The GCA maps are reported to have good glaucoma diagnostic ability, reaching sensitivity up to 99%, but with less than 80% of specificity.[4] Moreover, the deviation map shows the highest diagnostic sensitivity among GCA maps for early glaucoma detection, but at the same time, the highest rate of false-positive results.[4] These findings suggest that although GCA maps are highly sensitive, abnormal GCA maps do not necessarily indicate glaucoma-associated

http://dx.doi.org/10.1016/j.ophtha.2014.09.031
ISSN 0161-6420/14

retinal ganglion cell loss. This is a critical issue because general ophthalmologists tend to rely on the color-coded classification results.[5]

Previous studies have examined false-positive rates of OCT maps of GCA and RNFL analysis, but using a small number of patients,[6,7] and they included only certain OCT maps in analyses.[4,6–10] Therefore, the present study investigated the rate and associated factors of false-positive diagnostic classification of all available OCT maps (GCA along with RNFL) using SD-OCT. More importantly, we investigated the characteristic patterns of false-positive abnormalities on OCT deviation maps.

Methods

This study is based on the Macular Ganglion Cell Imaging Study, an ongoing prospective study of patients with glaucoma and healthy individuals at the Glaucoma Clinic of Seoul National University Hospital. Eyes were chosen from a database of healthy individuals. This study adhered to the Declaration of Helsinki and was approved by the institutional review board of Seoul National University Hospital.

Subjects

All 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 Corp, Tokyo, Japan), corneal pachymetry (POCKET II pachymeter echo graph; Quantel Medical, Clermont-Ferrand, France), slit-lamp biomicroscopy, gonioscopy, and dilated fundus examination. After maximum pupil dilation, all subjects were imaged by stereo optic disc photography, red-free RNFL photography (Vx-10; Kowa Optimed Inc, Tokyo, Japan) and SD-OCT (Cirrus-HD software version 6.0; Carl Zeiss Meditec Inc, Dublin, CA). They underwent standard automated perimetry using the Swedish interactive threshold algorithm with the 30-2 standard program (Humphrey Field Analyzer II; Carl Zeiss Meditec Inc).

For all subjects, the fovea-disc angle was measured using the overlay images of SD-OCT images and red-free RNFL photographs, as described previously.[11–13] The image of the RNFL deviation map was precisely overlaid on a red-free RNFL photograph with reference to the retinal vessels to compensate for the potential effects of ocular rotation on the fovea-disc angle. The fovea-disc angle was defined as the angle between the horizontal line thorough the disc center and the line connecting the fovea and the disc center on the overlay images (Fig 1).

Inclusion criteria were best-corrected visual acuity ≥20/25, an open angle on gonioscopic examination, absence of glaucomatous optic neuropathy, absence of RNFL defect according to red-free RNFL photography, and normal visual field. Absence of glaucomatous optic neuropathy was defined as a cup-to-disc ratio less than 0.6 and an intact neuroretinal rim without optic disc hemorrhages, notches, or localized pallor. Color disc and red-free RNFL images were evaluated by 2 independent observers (K.E.K. and J.W.J.) in a masked fashion, without knowledge of the clinical information. Only subjects with reliable examinations and visual fields (fixation loss <15%, false-positive error rates <15%, and false-negative error rates <15%) were included.

Exclusion criteria included a history of IOP >21 mmHg in either eye, using IOP-lowering medication in either eye, intraocular surgery in the study eye except simple cataract surgery, ocular inflammation or trauma, diseases that may cause optic neuropathy or RNFL damage, diseases that could affect the visual field, and diseases that may affect the peripapillary and macular area where OCT scans are obtained. Subjects were also excluded if they had abnormal visual fields defined as glaucoma hemifield test results outside normal limits, a pattern standard deviation with $P < 0.05$, or a cluster of ≥3 points in the pattern deviation plots in a single hemifield (superior or inferior) with $P < 0.05$, one of which has $P < 0.01$. In cases when both eyes were eligible, 1 eye was chosen randomly before analysis.

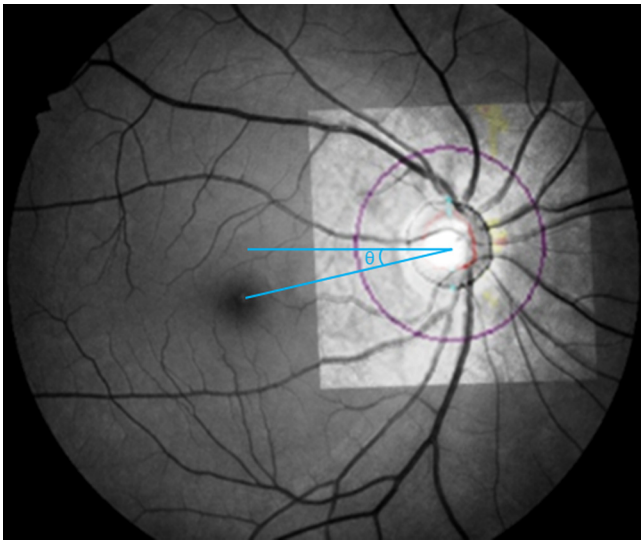

Figure 1. Fovea-disc angle was measured using overlay images consisting of spectral-domain optical coherence tomography (SD-OCT) images and red-free retinal nerve fiber layer (RNFL) photographs. The RNFL deviation map image was overlaid on the RNFL photograph with reference to retinal vessel trajectories. The fovea-disc angle (θ) was defined as the angle between the horizontal line thorough the disc center and the line connecting the fovea and the disc center on the overlay images.

Spectral-Domain Optical Coherence Tomography Measurements

All SD-OCT images were obtained by a single, well-trained technician using the Cirrus OCT device, the details of which have been described.[14] Only subjects with good-quality scans were included for analysis. Good-quality OCT images were defined as those with signal strength ≥8 (maximum = 10), without motion artifact, involuntary saccade, or overt misalignment of decentration and absence of algorithm segmentation failure.

One macular scan centered on the fovea (macular 200×200 cube protocol) and 1 peripapillary scan centered on the optic disc (optic disc 200×200 cube protocol) were acquired through dilated pupils. The automatically measured macular GCIPL thicknesses, RNFL thicknesses, and optic nerve head (ONH) parameters by GCA, RNFL analysis, and ONH analysis, respectively, were used in the analyses. For both the right and left eyes, 12 o'clock corresponded to the superior region, 3 o'clock corresponded to the nasal region, 6 o'clock corresponded to the inferior region, and 9 o'clock corresponded to the temporal region. Right-eye orientation was used for documenting all of the OCT data.

The GCA algorithm detects and measures macular GCIPL thickness 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 GCA provides thickness parameters of average, minimum, and 6 sectors