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Automated Detection of Hemifield Difference across Horizontal Raphe on Ganglion Cell–Inner Plexiform Layer Thickness Map

Young Kook Kim, MD,[1] *Byeong Wook Yoo, BE,*[2] *Hee Chan Kim, PhD,*[3] *Ki Ho Park, MD, PhD*[1]

Purpose: A MATLAB-based (The MathWorks, Inc, Natick, MA) computer program (the ganglion cell-inner plexiform layer [GCIPL] hemifield test) for automated detection of GCIPL thickness difference across the horizontal raphe was developed, and its glaucoma diagnostic performance was assessed.

Design: Cross-sectional study.

Participants: A total of 65 eyes of normal, healthy subjects along with 162 eyes of patients with glaucoma (79 preperimetric and 83 early perimetric).

Methods: Cirrus high-definition optical coherence tomography (HD-OCT) (Carl Zeiss Meditec, Dublin, CA) was used to scan all of the subjects' macular and optic discs. A positive (i.e., "outside normal limits") GCIPL hemifield test result was declared if the following 3 conditions were all met: (1) The reference line (a horizontal line dividing the superior and inferior hemifields) is continuously detected for longer than one-half of the distance from the temporal inner elliptical annulus to the outer elliptical annulus; (2) the average GCIPL thickness difference within 10 pixels of the reference line, both above and below, is $\geq$5 μm; and (3) the average RGB color ranges of the 10 pixels above and below the reference line display blue in 1 hemifield and red/yellow/white in the other hemifield.

Main Outcome Measures: Comparison of diagnostic ability using the areas under the receiver operating characteristic curves (AUCs).

Results: A positive GCIPL hemifield test result was observed more frequently in the glaucomatous eyes (74/79 preperimetric, 78/83 early perimetric) than in the normal eyes (1/65). In the preperimetric group, the AUC of the GCIPL hemifield test (0.967; sensitivity 94.94%, specificity 98.46%) was greater than that of the minimum GCIPL thickness (0.933), the inferotemporal GCIPL thickness (0.907), and the average GCIPL thickness (0.899) ($P = 0.09$, 0.06, and 0.03, respectively). In the early perimetric group, the AUC of the GCIPL hemifield test (0.962; sensitivity 93.98%, specificity 96.46%) was greater than that of the inferotemporal GCIPL thickness (0.938), the minimum GCIPL thickness (0.919), and the average GCIPL thickness (0.912) ($P = 0.38$, 0.17, and 0.11, respectively).

Conclusions: For discrimination of early glaucomatous structural loss, most notably in preperimetric glaucoma cases, identification of the GCIPL thickness difference across the horizontal raphe was effective. *Ophthalmology 2015;122:2252-2260 © 2015 by the American Academy of Ophthalmology.*

Glaucomatous structural and functional changes require timely evaluation and detection to prevent possible blindness. Because glaucoma primarily affects the retinal ganglion cells and their axons, measurement of the thickness of ganglion cell layers or retinal nerve fiber layers (RNFLs) has proved an effective glaucoma detection strategy.[1–5]

Ganglion cell analysis (GCA) is a new Cirrus high-definition optical coherence tomography (HD-OCT) (Carl Zeiss Meditec, Dublin, CA) algorithm developed for macular ganglion cell-inner plexiform layer (GCIPL) thickness measurement.[6] The ability of the macular GCIPL parameters to discriminate between normal eyes and eyes with glaucoma was reported to be comparable to the circumpapillary RNFL and optic nerve head parameters.[5,7,8] However, GCIPL thickness, because of the large value range overlap between normal eyes and eyes with early glaucoma,[8–13] is known to be less sensitive and less specific than optic disc or circumpapillary RNFL thickness.[10–12,14]

For well-known anatomic reasons, glaucomatous visual field loss most commonly is not symmetric across the horizontal meridian.[15–17] Thus, hemifield comparative techniques, for example, the glaucoma hemifield test, often have been used for the detection of glaucomatous change.[16–18] Likewise, structural glaucomatous loss is often asymmetric, especially in the early stages of glaucoma.[9,19–21] Correspondingly, a useful approach is to observe, on a Cirrus HD-OCT GCIPL thickness map, the step-like configuration of the GCIPL thickness near the horizontal raphe. However, as a clinical glaucoma diagnostics strategy, this has generated little interest, probably because of the absence of objective configuration evaluation standards.

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This study was undertaken to develop a new algorithm for automated evaluation of a single macular GCIPL thickness map and detection of hemifield difference across the horizontal raphe for identification of early glaucoma.

Methods

This study was approved by the Seoul National University Hospital Institutional Review Board and adhered to the tenets of the Declaration of Helsinki.

Subjects

All of the study subjects were examined between December 2012 and January 2014 at the Seoul National University Hospital Glaucoma Clinic in Seoul, Korea. Eligible participants were consecutively enrolled on the basis of a retrospective medical record review. All underwent a complete ophthalmic examination, including visual acuity assessment, refraction, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry (Haag-Streit, Koniz, Switzerland), and dilated stereoscopic examination of the optic disc. They also underwent central corneal thickness measurement (Orbscan 73 II, Bausch & Lomb Surgical, Rochester, NY), axial length measurement (IOLMaster ver. 5, Carl Zeiss Meditec, Dublin, CA), red-free RNFL photography, optic nerve head and macular imaging by Cirrus HD-OCT (Carl Zeiss Meditec), and a central 30-2 threshold test of the Humphrey Visual Field (HFA II; Humphrey Instruments Inc, Dublin, CA).

For inclusion, subjects were required to have a best-corrected visual acuity ≥20/40 in the Snellen equivalent, spherical refraction >−6 diopters (D) and <3 D, a normal open anterior chamber angle, and reliable visual field tests. Individuals were excluded from further analysis on the basis of the following criteria: (1) the existence of a secondary cause of glaucomatous optic neuropathy; (2) a history of intraocular surgery (except cataract surgery) or retinal laser photocoagulation; and (3) any neurologic and systemic diseases that could affect retina and visual field results. One eye was randomly selected if both eyes were found to be eligible.

Glaucomatous eyes were defined by the presence of characteristic optic disc (localized or diffuse neuroretinal rim thinning) on stereo disc photograph or the presence of RNFL defect on red-free fundus imaging, regardless of the presence or absence of glaucomatous visual field defects. Eyes with glaucomatous visual field defects were defined as (1) a cluster of 3 points with probabilities <5% in at least 1 hemifield on the pattern deviation map, including at least 1 point with a probability <1% or a cluster of 2 points with a probability <1%; (2) glaucomatous hemifield test results outside of the normal limits; or (3) a pattern standard deviation beyond 95% of the normal limits, as confirmed by at least 2 reliable examinations (false-positive/negatives <15%, fixation losses <15%).

The healthy controls had an intraocular pressure (IOP) ≤21 mm Hg, no IOP elevation history, no glaucomatous optic disc appearance, no RNFL defects, and normal visual field test results. On the basis of visual field test results, patients with glaucoma were divided into 2 groups: preperimetric glaucoma (normal visual field) and early perimetric glaucoma (visual field mean deviation [MD] >−6 decibels [dB]). The appearance of the optic disc on stereoscopic photographs and that of RNFL on red-free imaging were evaluated by 2 glaucoma specialists (Y.K.K. and K.H.P.) who were masked to all other information on the eyes. Discrepancies between the 2 observers' findings were resolved by consensus.

Cirrus High-Definition Optical Coherence Tomography Optic Disc Cube

Optic disc (Optic Disc Cube 200×200 protocol) and macular scans (Macular Cube 512×128 protocol) using Cirrus HD-OCT instrument software (version 6.0) for RNFL and GCIPL thickness measurements, respectively, were carried out. Poor-quality images showing eye motion, blinking artifacts, or poor centration were discarded by the examiner, and those with a signal strength <6 were excluded from the study. The circumpapillary RNFL thicknesses were measured overall, in each of the 4 quadrants, and in each of the 12 clock-hour sectors. The average, minimum, and 6 sectoral (superotemporal, superior, superonasal, inferonasal, inferior, inferotemporal) GCIPL thicknesses in an elliptical annulus were measured in the macular cube scan mode.[5,22]

Ganglion Cell-Inner Plexiform Layer Hemifield Test

The GCIPL thickness maps were processed using the GCIPL Hemifield Test (Medical Electronics Lab, Seoul National University, Seoul, Korea), a customized software in MATLAB (2013a version, The MathWorks, Inc, Natick, MA). The GCIPL Hemifield Test automatically extracted, from the GCIPL thickness map, a 32-bit color-scale image of an elliptical annulus of 2.0 mm vertical outer radius and 2.4 mm horizontal outer radius. Then, automated image processing for line detection was conducted. The GCIPL Hemifield Test uses the Hough transform algorithm to detect lines on a GCIPL thickness map. Hough transform is a widely used technique in the image processing field for detection of lines according to their parametric representation. In general, to implement the Hough transform, the threshold is selected heuristically. Setting the threshold too low or too high can give rise to false positivity or mis-detection, respectively, for a given shape. According to the threshold, it was determined whether the small gaps in line segments were automatically filled or not. Subsequently, the end points of the line segments corresponding to the peaks in the Hough transform were found.

Subsequent image processing for detection of color values was conducted only in cases in which horizontal reference lines longer than one-half the distance from the temporal inner elliptical annulus to the outer elliptical annulus were successfully detected. The red, green, and blue (RGB) color values of the pixels above and below the detected line dividing the superior and inferior hemifields were discriminated. They were converted to GCIPL thicknesses on the basis of the GCIPL thickness map's reference color bar. Ultimately, a positive (i.e., "outside normal limits") GCIPL Hemifield Test result was declared if the following 3 conditions were all met: (1) The reference line (a horizontal line dividing the superior and inferior hemifields) is continuously detected for longer than one half of the distance from the temporal inner elliptical annulus to the outer elliptical annulus; (2) the average GCIPL thickness difference within 10 pixels of the reference line, both above and below, is ≥5 μm; and (3) the average RGB color ranges of the 10 pixels above and below the reference line display blue in 1 hemifield and red/yellow/white in the other hemifield (Figs 1 and 2).

Optimal Cutoff Values for Ganglion Cell-Inner Plexiform Layer Hemifield Test

The optimal cutoff values for classifying cases as positive or negative were confirmed by using the areas under the receiver operating characteristic curves (AUCs) as the following process. First, the probable diagnostic criteria for discriminating early glaucoma was postulated that calculation of the average GCIPL thickness difference is within approximately 10 pixels both above and below the reference line and the baseline of the difference is ≥7 μm. Thus, the