Differentiation of Compressive from Glaucomatous Optic Neuropathy with Spectral-Domain Optical Coherence Tomography

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Purpose: To compare optic disc topography in eyes with compressive optic neuropathy (CON) and open-angle glaucoma (OAG) using spectral-domain (SD) optical coherence tomography (OCT) and Heidelberg retinal tomograph (HRT) (Heidelberg Engineering GmbH, Heidelberg, Germany).

Design: Cross-sectional, observational study.

Participants: A total of 200 eyes from 123 patients with CON (69 eyes) or OAG (58 eyes) and controls (73 eyes).

Methods: Univariate and multivariate analyses of HRT parameters, SD-OCT circumpapillary retinal nerve fiber layer (RNFL) thickness, and optic nerve head (ONH) parameters.

Main Outcome Measures: Circumpapillary RNFL, OCT ONH parameters, and HRT parameters.

Results: The univariate analysis of OCT parameters demonstrated significant differences between the temporal and nasal quadrants; clock hours 3 (55 vs. 73 μm), 4, 8 (93.9 vs. 70.7 μm), 9, and 10; vertical cup-to-disc ratio (C:D) (0.6 vs. 0.8) and cup volume (0.2 vs. 0.5) ($P<0.001$) between patients with CON and OAG, respectively. The CON discs were significantly different from normal discs for all OCT parameters except cup volume. The CON discs were not significantly different from normal discs for HRT parameters, except for mean RNFL thickness and cup shape measure. The OAG discs were significantly different from normal discs in all HRT and OCT parameters ($P<0.001$). Multivariate analysis demonstrated that the OCT 3 o'clock temporal sector, average C:D ratio, vertical C:D ratio, and cup volume measurements were able to differentiate OAG from CON.

Conclusions: Compressive optic neuropathy is associated with significantly thinner nasal and temporal sectors compared with OAG, whereas OAG results in larger cups and cup volume with OCT measurements. The Heidelberg retinal tomograph is not able to differentiate CON from normal discs. *Ophthalmology 2014;■:1–8 © 2014 by the American Academy of Ophthalmology.*

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Optic neuropathies produce changes in the optic nerve head (ONH) that reflect the underlying cause. However, significant overlap exists between different types of optic nerve injuries. For example, although excavation and enlargement of the optic cup are common features of glaucomatous optic neuropathy, other optic neuropathies, including compressive optic neuropathy (CON), have been reported to produce similar morphologic changes.[1–24]

Both glaucoma and CON are generally slowly progressive processes. However, the site of injury is different. In glaucoma, it is at the optic disc, whereas in CON, it is at the intraorbital or intracranial optic nerve or chiasm. The morphologic differences in the ONH appearance between these conditions have been evaluated primarily using color photographs. "Cupping" or excavation of the ONH has been described to occur in CON and is often said to resemble glaucomatous optic nerve changes, although these findings have been minimally documented using objective quantitative measures. Several authors have highlighted the difficulty in distinguishing glaucomatous optic neuropathy from CON, especially in cases of "normal pressure glaucoma."[15,16]

We extend the analysis between these 2 groups of optic neuropathies using both confocal scanning laser ophthalmoscopy with the Heidelberg retinal tomograph (HRT) (Heidelberg Engineering GmbH, Heidelberg, Germany) and spectral-domain (SD) optical coherence tomography (OCT) to objectively evaluate the differences in ONH morphology.

Methods

Patient Selection

This study adhered to the Declaration of Helsinki and was approved and monitored by the institutional review boards of the Northern Regional Ethics Committee. Patients who met the entrance criteria for the diagnoses of open-angle glaucoma (OAG) (secondary glaucomas were excluded) or CON and normal controls

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were enrolled in the study. The criteria described by Foster et al[25] were used, including open angles by gonioscopy and a specifically defined cup-to-disc ratio (C:D) and visual field loss in at least 1 eye. The field loss was defined as glaucoma if the glaucoma hemifield test result was outside normal limits and 3 points were abnormal at the 5% level in 1 hemifield on the pattern deviation plot of a Humphrey Field Analyzer (HFA 2; Carl Zeiss Meditec, Inc., Dublin, CA), according to the Swedish Interactive Threshold Algorithm standard 24-2 program. All patients with OAG had been regularly attending the glaucoma clinic for at least 3 years. Patients were excluded if they demonstrated features that are atypical for glaucoma, including Ishihara color plate abnormality (patients had to identify 13/14 color plates), visual field abnormalities inconsistent with glaucoma (temporal field loss greater than nasal, bitemporal pattern, central scotoma), and visual acuity <20/25. Patients with OAG can be divided into those who presented with an intraocular pressure (IOP) <20 mmHg before treatment (n = 41) (normal tension glaucoma) and those who presented with IOP ≥21 mmHg (n = 17).

All patients with CON underwent a complete neuro-ophthalmic assessment and had tumors confirmed with magnetic resonance imaging. Subjects were included if they had an HRT of adequate quality, 24-2 visual field test, and OCT of the peripapillary nerve fiber layer all within a 6-week period. All patients were at least 1 year from any surgical intervention because it is recognized that mean deviation (MD) losses can be reversible after surgery to relieve compression, suggesting the decrease in MD is not due to retinal ganglion cell (RGC) loss but due to RGC dysfunction. When both eyes of a subject qualified for inclusion, data from both eyes were used with appropriate statistical adjustment (see "Statistical Analysis"). Patients in the CON and control groups were excluded if they had an IOP greater than 21 mmHg or a family history of OAG. Both patients with glaucoma and patients with CON had to meet the following inclusion criteria: spherical refraction within 5.0 diopters of emmetropia and cylinder correction of less than 3.0 diopters; no other significant ocular disease; no or minimal lens opacity; no optic disc abnormalities, such as tilted disc or peripapillary atrophy; no history of intraocular surgery other than cataract surgery; and no systemic disease that could affect optic disc configuration, such as diabetes mellitus.

Examination and Testing

Demographic information was recorded, including age, sex, racial derivation (Caucasian, Asian, or other), and history of cataract surgery. For patients with OAG, the IOP before starting treatment was included, as was the IOP at the time of recruitment. Subjects underwent a complete ocular examination, including Snellen visual acuity, Goldmann applanation tonometry, gonioscopy, slit-lamp examination, and dilated fundus examination. The refractive error used was the presenting eyeglass correction. Each enrolled eye also underwent visual field testing with the HFA Swedish Interactive Threshold Algorithm standard 24-2, OCT examination of the peripapillary retinal nerve fiber layer (RNFL) (RNFL and ONH: Optic Disc Cube 200×200, Cirrus OCT; Carl Zeiss Meditec, Inc.), and scanning laser ophthalmoscopy with HRT-3 (Eye Explorer software version 1.5.1.0; Heidelberg Engineering GmbH).

Patients were included if the visual field test result met the reliability criteria and their OCT scans were of good quality (signal strength >7 on 3 consecutive scans). We compared disc area in phakic eyes with the measurements in pseudophakic eyes to evaluate whether refraction could affect the results. There was no significant difference between the groups (data not shown). This supports the concept that optical differences did not substantially bias the disc diameter measurement.

Visual Fields

Visual fields were deemed to be reliable if they met the following criteria: fixation loss less than 20% and false-positive and false-negative error less than 33%. For the control group, a normal visual field was defined by Anderson and Patella: no 3 contiguous points of $P<5\%$ on the pattern deviation probability plot, no corrected pattern standard deviation of $P<5\%$, and a normal glaucoma hemifield test result.[26]

Heidelberg Retinal Tomograph

All participants underwent imaging analyses with an HRT (software version 3.04; Heidelberg Engineering GmbH). For each HRT imaging session, 3 images were obtained for each eye by an experienced examiner. After generating a mean topographic image, the disc margin was delineated as a contour line by the same observer. The HRT software had to be able to analyze the images, and the standard deviation of the 3 scans making up each study had to be <50 mm^2.

Optical Coherence Tomography

All participants underwent OCT measurement of RNFL thickness and optic disc measurements for each eye using the Cirrus OCT (OCT-3, OCT 4.0 software; Carl Zeiss Meditec Inc.). The RNFL and ONH Optic Disc Cube 200×200 scan protocol was used to evaluate subjects' nerve fiber layer. Good-quality scans were defined as signal strength ≥7 (maximum 10), optic disc centering, and uniform brightness across the scan circumference. If a participant's pupils were large enough to permit adequate OCT imaging (≥5 mm diameter), scanning was completed without the use of mydriatic eye drops. The OCT, visual field, and eye examinations were completed within a 6-week period in all patients.

Statistical Analysis

Demographics of the 3 groups were compared pairwise using the *t* test for age and Fisher exact test for eye laterality (right, left, both), sex, and ethnicity. Some participants enrolled in the study had data from both eyes used in the analyses. Therefore, generalized estimating equations (GEEs)[15] using a Gaussian distribution were used to compare the 3 diagnostic groups with respect to the individual eye parameters. The GEEs account for the within-group correlations introduced when some participants contribute data from both eyes. To compare the differences in HRT parameters among groups, while also controlling for the total amount of damage, GEE models were used with the HRT parameter as the dependent variable and HFA MD, HRT disc area, and HRT reference plane height as covariates. Separate models were created with the following dependent variables: cup area, rim area, C:D area, cup volume, rim volume, mean cup depth, cup-shape measure, and vertical C:D. The HFA MD was included as a covariate to control for the total amount of damage in the eye and disc area because it is related to other disc measures.[26,27] The reference plane height also was included because there may be a greater proportionate loss of macular RNFL in CON compared with OAG.[28] The statistical significance for the regression analyses was based on a Bonferroni-adjusted significance level for the overall comparison among the 3 diagnosis groups. This adjusted significance level was derived from the numbers of parameters compared for each regression set. Only when this group effect was nominally significant were pairwise comparisons undertaken among the 3 diagnosis groups. All statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL).

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