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Diagnostic Accuracy of the Spectralis and Cirrus Reference Databases in Differentiating between Healthy and Early Glaucoma Eyes

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Purpose: To evaluate and compare the diagnostic accuracy of global and sector analyses for detection of early visual field (VF) damage using the retinal nerve fiber layer (RNFL) reference databases of the Spectralis (Heidelberg Engineering, Heidelberg, Germany) and Cirrus (Carl Zeiss Meditec, Dublin, CA) spectral-domain optical coherence tomography (SD OCT) devices.

Methods: Healthy subjects and glaucoma suspects from the Diagnostic Innovations in Glaucoma Study (DIGS) and African Descent and Glaucoma Evaluation Study (ADAGES) with at least 2 years of follow-up were included. Global and sectoral RNFL measures were classified as within normal limits, borderline (BL), and outside normal limits (ONL) on the basis of the device reference databases. The sensitivity of ONL classification was estimated in glaucoma suspect eyes that developed repeatable VF damage.

Results: A total of 353 glaucoma suspect eyes and 279 healthy eyes were included. A total of 34 (9.6%) of the glaucoma suspect eyes developed VF damage. In glaucoma suspect eyes, Spectralis and Cirrus ONL classification was present in 47 eyes (13.3%) and 24 eyes (6.8%), respectively. The sensitivity of the global RNFL ONL classification among eyes that developed VF damage was 23.5% for Cirrus and 32.4% for Spectralis. The specificity of within-normal-limits global classification in healthy eyes was 100% for Cirrus and 99.6% for Spectralis. There was moderate to substantial agreement between Cirrus and Spectralis classification as ONL.

Conclusions: The Spectralis and Cirrus reference databases have a high specificity for identifying healthy eyes and good agreement for detection of eyes with early glaucoma damage. *Ophthalmology 2015;■:1–7 © 2015 by the American Academy of Ophthalmology.*

Glaucoma is a progressive optic neuropathy characterized by loss of retinal ganglion cells and associated morphologic changes to the optic nerve and retinal nerve fiber layer (RNFL).[1] For many patients, structural changes in the neuroretinal rim and RNFL precede the detection of visual field (VF) deficits in early glaucoma,[2,3] emphasizing that structural assessment of the optic nerve is an essential component of timely glaucoma diagnosis and management.[4–8]

The last 2 decades have seen a proliferation of imaging instruments that provide objective and quantitative measures of retinal tissue that cannot be assessed with standard fundus photography. Most recently, spectral-domain optical coherence tomography (SD OCT) has allowed clinicians to obtain unprecedented high-resolution images of the optic nerve head and RNFL, and has become the standard of care for the management of many ophthalmic conditions.[9,10] Spectral-domain OCT instruments often use proprietary reference databases comprising measurements of healthy eyes to set limits of normality for optic disc, RNFL, and ganglion cell measurements. Classification as within normal limits (WNL), borderline (BL), and outside normal limits (ONL) provides clinicians with a reference for making clinical decisions.[11]

In the United States, the Food and Drug Administration regulates the commercialization of the reference databases, but there are no standards or guidelines for the types or numbers of subjects that should be included or how the data should be analyzed or presented in the reference databases.[12] In addition, there is sparse literature evaluating the accuracy of the reference database algorithms for detection of glaucomatous structural damage, with reports of false-positive RNFL results in healthy eyes.[13,14] Moreover, to our knowledge, there are no published reports comparing the agreement between different SD OCT instruments when their specific databases are used to classify glaucoma and healthy eyes.

The purpose of this study is to evaluate and compare the diagnostic accuracy of Spectralis (Heidelberg Engineering, Heidelberg, Germany) and Cirrus (Carl Zeiss Meditec, Dublin, CA) SD OCT global and sector RNFL classification for the detection of early glaucomatous changes.

Methods

Description of Study Population

This was an observational cross-sectional study. Healthy participants and glaucoma suspects without repeatable VF damage at baseline with at least 2 years of follow-up were included from 2 prospective longitudinal studies designed to evaluate optic nerve

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structure and visual function in glaucoma: the African Descent and Glaucoma Evaluation Study (ADAGES) and the Diagnostic Innovations in Glaucoma Study (DIGS). The 3-site ADAGES collaboration includes the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California, San Diego (Data Coordinating Center); New York Eye and Ear Infirmary; and Department of Ophthalmology, University of Alabama at Birmingham. The DIGS includes only patients recruited at University of California, San Diego, and uses protocols identical to that of ADAGES. Methodological details have been described.[15] Institutional review board/ethics committee approval was obtained. Written informed consent was obtained from all participants. The institutional review boards and human subjects committees of all 3 sites (University of California, San Diego, CA; New York Eye and Ear Infirmary, New York, NY; and University of Alabama at Birmingham, Birmingham, AL) approved all methods used to conduct this study. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects and to the Health Insurance Portability and Accountability Act. The DIGS and ADAGES were registered at http://cilincaltrials.gov (NCT00221897 and NCT00221923, respectively) on September 14, 2005.

All subjects had open angles on gonioscopy. Subjects were excluded if they presented at study entry with a best-corrected visual acuity less than 20/40, spherical refraction greater than 5.0 diopters (D) or cylinder correction greater than 3.0 D, or any other ocular or systemic disease that could affect the optic nerve or the VF.

All subjects underwent an annual comprehensive ophthalmologic examination including review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, dilated funduscopic examination, and stereoscopic optic disc photography. Semi-annual examination included intraocular pressure (IOP), SD OCT imaging, and VF testing.

Healthy subjects were recruited from the general population through advertisements, from family members of patients, and from primary eye care clinics at the 3 study centers. Healthy eyes had an IOP of 21 mmHg or less with no history of elevated IOP, a healthy-appearing optic disc, and no VF abnormalities (pattern standard deviation within 95% confidence limits and a glaucoma hemifield test result WNL). Glaucoma suspect eyes were defined as eyes with ocular hypertension (OHT) (IOP >21 mmHg in the presence of a healthy-appearing optic disc and normal VF), a history of elevated IOP, or an optic disc appearance suspicious of glaucoma (neuroretinal rim thinning or RNFL defects on masked simultaneous stereophotograph assessment) in the presence of a normal VF at the time of SD OCT imaging.[15]

An abnormal VF result was defined as having a pattern standard deviation outside the 95% confidence limits or a glaucoma hemifield test result outside the reference range on the Swedish Interactive Threshold Algorithm (Standard 24-2) of the Humphrey VF analyzer (Carl Zeiss Meditec, Inc., Dublin, CA). An optic disc suspicious of glaucomatous optic neuropathy was defined as suspicion of neuroretinal rim thinning or RNFL defects on masked simultaneous stereophotograph assessment by 2 experienced graders. Adjudication or consensus grading resolved disagreements in photograph assessment.

Standard Automated Perimetry

All patients underwent VF testing using the Swedish Interactive Threshold Algorithm Standard 24-2 strategy within 30 days of SD OCT imaging. All VFs were evaluated by the University of California, San Diego, Visual Field Assessment Center.[16] Visual fields with more than 33% fixation losses or false-negative errors, or more than 15% false-positive errors, were excluded. The only exception was the inclusion of VFs with false-negative errors of more than 33% when the field showed advanced disease (VF mean deviation <−12 decibels [dB]). Visual fields exhibiting a learning effect (i.e., initial tests showing consistent improvement on VF indices) were also excluded. Visual fields were further reviewed for the following artifacts: lid and rim artifacts, fatigue effects, inappropriate fixation evidence that the VF results were due to a disease other than glaucoma (e.g., homonymous hemianopia), and inattention.

Optical Coherence Tomography

Each subject was required to have a good-quality Cirrus SD OCT and a Spectralis SD OCT acquired on the same day. The most recent good-quality images (as determined by the Imaging Data Analysis and Evaluation [IDEA] Reading Center) were included in the analysis for nonprogressing eyes. Images obtained within 6 months of the date on which progression was detected were included for progressing eyes that developed VF damage.

The Cirrus SD OCT uses a superluminescent diode laser with a center wavelength of 840 nm and an acquisition rate of 27 000 A-scans per second.[17] The protocol used for RNFL thickness evaluation was the optic disc cube. This protocol is based on a tridimensional scan of a 6×6-mm^2 area centered on the optic disc, where information from a 1024 (depth)×200×200-point parallelepiped is collected. Image acquisition time is approximately 2 seconds. Parapapillary RNFL thickness is measured along a 3.46-mm-diameter circle automatically placed around the optic disc; approximately 362 A-scans are sampled to obtain these RNFL parapapillary measurements. On the basis of the IDEA Center review, well-centered scans with signal strength ≥7 and the absence of movement artifact were included.

The Cirrus SD OCT algorithm provides RNFL thickness measurement of the global, superior, nasal, inferior, temporal, and 12 clock-hour sectors along the measurement circle.[2] The patient's RNFL scan results are compared with reference data and presented as color-coded maps. The Cirrus age-adjusted reference database has been described.[18] In short, it comprises 284 healthy white subjects (43%) and Asian (24%), African (18%), Hispanic (12%), and Indian (1%) subjects between the ages of 19 and 84 years. Subjects with IOP >21 mmHg, refractive error outside the range of −12 to 8 D, evidence of VF damage, or RNFL defect or disc hemorrhage were not included in the reference database.[18] White, green, yellow, and red are color codes that depict RNFL thicknesses relative to the reference database. The RNFL thickness values that are higher (H) than the 95% of the reference database measurements are white, values that are within normal limits (WNL) of the 95% of reference database measurements are green, and values that are thinner than the reference database range at the 5% level (BL) are yellow. The RNFL thickness values that are thinner than the reference database range at the 1% level (ONL) are red. Sector ONL was defined as at least 1 of 12 Cirrus clock hours classified as ONL.

Spectralis OCT uses a dual-beam SD OCT, a confocal laser-scanning ophthalmoscope with a wavelength of 870 nm, and an infrared reference image to obtain images of ocular microstructures.[17] The instrument has an acquisition rate of 40 000 A-scans per second. Spectralis OCT incorporates a real-time eye-tracking system that couples confocal laser-scanning ophthalmoscope and SD OCT scanners to adjust for eye movements and to ensure that the same location of the retina is scanned over time. The protocol used was the high-resolution RNFL circle scan, which consists of 1536 A-scan points from a 3.45-mm circle centered on the optic disc. All patients had their corneal curvature input into the machine before the examination. These A-scans are averaged into 768 data points. Image acquisition time is approximately 3 seconds. The scan time varies because of the Spectralis eye tracking