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Risk of Visual Field Progression in Glaucoma Patients with Progressive Retinal Nerve Fiber Layer Thinning

A 5-Year Prospective Study

Marco Yu, PhD,[1,2] *Chen Lin, BM,*[1] *Robert N. Weinreb, MD,*[3] *Gilda Lai, BSc,*[1] *Vivian Chiu, BSc,*[1] *Christopher Kai-Shun Leung, MB ChB, MD*[1]

Purpose: To investigate whether progressive retinal nerve fiber layer (RNFL) thinning is predictive of progressive visual field (VF) loss in glaucoma.

Design: Prospective study.

Participants: A total of 139 primary open-angle glaucoma patients (240 eyes) followed up for ≥5 years.

Methods: Retinal nerve fiber layer imaging and VF testing were performed at ~4-month intervals. Progressive RNFL thinning was determined by event analysis (Guided Progression Analysis [GPA]) and trend analysis (Trend-based Progression Analysis [TPA]) of serial registered RNFL thickness maps. VF progression was detected according to the Early Manifest Glaucoma Trial (EMGT) ("likely progression") and pointwise linear regression (PLR) criteria (≥3 contiguous locations with sensitivity change <0 decibels [dB]/year at $P < 0.01$). Hazard ratios (HRs) for predicting VF progression were calculated by Cox proportional hazard modeling with progressive RNFL thinning as a time-dependent covariate. The specificity of GPA/TPA for detection of RNFL changes was determined by the proportion of eyes with significant RNFL thinning/thickening in 25 normal subjects followed weekly for 8 consecutive weeks and the proportion with significant RNFL thickening in the glaucoma group.

Main Outcome Measures: The HRs of VF progression.

Results: A total of 65 (27.1%) and 117 eyes (48.8%) had progressive RNFL thinning based on GPA and TPA, respectively, and 30 (12.5%) and 39 eyes (16.3%) had VF progression per the EMGT and PLR criteria, respectively, during follow-up. Eyes with progressive RNFL thinning had lower VF survival estimates and a faster decline of visual field index than eyes without. Progressive RNFL thinning predicted the development of VF progression with HRs of 8.44 (95% confidence interval, 3.30−21.61) (EMGT criteria) and 5.11 (2.51−10.42) (PLR criteria) for TPA and 3.95 (1.74−8.93) (EMGT criteria) and 3.81 (1.83−7.92) (PLR criteria) for GPA after controlling for baseline covariates. The specificities of GPA and TPA were 100% (83.4%−100.0%) in the normal group and 81.7% (76.2%−86.4%) and 84.2% (78.9%−88.6%), respectively, in the glaucoma group.

Conclusions: Progressive RNFL thinning determined by GPA and TPA is predictive of detectable functional decline in glaucoma. This finding underscores the significance of detecting progressive RNFL thinning and its relevance to initiate or augment treatment for glaucoma patients. Regulatory authorities may consider progressive RNFL thinning as an outcome measure in clinical trials for evaluation of glaucoma treatment. *Ophthalmology 2016;■:1−10 © 2016 by the American Academy of Ophthalmology.*

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Glaucoma is the most common form of optic neuropathy with an estimated global prevalence of 64.3 million in 2013.[1] As a leading cause of irreversible blindness, early detection of optic nerve degeneration with initiation or augmentation of glaucoma treatment prevents progressive loss in vision in patients with glaucoma.[2,3] Although evaluation of progressive decline in neuronal structure and function often is difficult in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, progressive loss of the retinal ganglion cell axons in glaucoma can be objectively and reproducibly measured as progressive thinning of the retinal nerve fiber layer (RNFL) with optical imaging technologies, including scanning laser polarimetry and optical coherence tomography (OCT).[4,5] Yet, detectable structural and functional changes of the optic nerve may not be evident simultaneously,[6,7] and the

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implication of detecting progressive RNFL thinning in the management of patients with glaucoma remains unclear. The primary outcome measure for evaluation of glaucoma progression in all landmark glaucoma treatment trials largely has been predicated on visual field (VF) assessment.[8] Regulatory authorities, such as the US Food and Drug Administration, consider structural changes of the optic nerve to be an outcome measure for the evaluation and approval of treatment to delay glaucoma progression only when there is evidence that the new outcome measure predicts functional change that is clinically relevant to a patient.[9] Identifying structural biomarkers that predict functional change of the optic nerve is an unmet need in glaucoma management.

Since its introduction in 2006, spectral-domain or Fourier-domain OCT has gained popularity over other optical imaging technologies in monitoring RNFL loss in glaucoma because of its superior resolution to discern the individual retinal layers. Spectral-domain OCT RNFL measurement has been shown to have a lower test–retest variability compared with time-domain OCT[10] and outperforms time-domain OCT and scanning laser polarimetry to detect progressive RNFL thinning.[5,11] With a high scan speed, topographic analysis of the RNFL over an optic disc region of approximately 6×6 mm^2 is possible.[12] Progressive RNFL thinning missed by the conventional circumpapillary RNFL assessment can be revealed in the RNFL thickness map.[13] Given that glaucomatous RNFL defects often can be observed before detectable VF defects, we hypothesize progressive RNFL thinning, determined by (1) Guided Progression Analysis (GPA) (Carl Zeiss Meditec, Dublin, CA) (an event-based algorithm) and (2) Trend-based Progression Analysis (TPA) (a trend-based algorithm) of the RNFL thickness maps, to be predictive of VF progression in patients with glaucoma.

Methods

Subjects

Between July 2007 and October 2015, 139 patients with primary open-angle glaucoma were consecutively recruited from the Caritas Medical Center, Hong Kong Eye Hospital, and the University Eye Center of the Chinese University of Hong Kong. They were followed up every 4 months for at least 5 years at the University Eye Center for RNFL imaging and perimetry. All subjects had a complete ophthalmic examination, including measurement of best-corrected visual acuity, axial length (partial coherence laser interferometry; Carl Zeiss Meditec), central corneal thickness (CCT) (ultrasound pachymetry), intraocular pressure (IOP) (Goldmann applanation tonometry), gonioscopy, and biomicroscopy examination of the optic disc and retina. Inclusion criteria included best-corrected visual acuity ≥20/40 and having ≥5 years of longitudinal follow-up. Subjects with non-glaucomatous VF loss were excluded from the study at baseline, and it was checked during the study follow-up. No causes other than glaucoma could be identified that were accountable for the RNFL or VF loss observed in the study. Glaucoma was diagnosed by the presence of optic disc excavation and narrowed neuroretinal rim as determined by the ISNT rule[14] with slit-lamp biomicroscopy and corresponding VF defects in standard automated perimetry (described later) in at least 1 eye independent of the levels of IOP. All patients with glaucoma had RNFL imaging and VF testing for both eyes at ~4-month intervals. They were treated during the study follow-up with reference to the target IOP determined by the attending ophthalmologists without considering the analysis of progressive RNFL thinning. Twenty-five healthy subjects also were consecutively enrolled during the study period and followed up weekly for 8 consecutive weeks for RNFL imaging and VF testing in 1 randomly selected eye to determine the specificity of GPA and TPA detection of progressive RNFL thinning. These subjects had no optic disc abnormalities in clinical examination, no RNFL abnormalities on spectral-domain OCT, no VF abnormalities on VF testing, and no history of ocular disease (except for early cataract), neurologic disease, or major systemic illness. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and was approved by the local research ethics committee, with informed consent obtained.

Optical Coherence Tomography Retinal Nerve Fiber Layer Imaging

The Cirrus HD-OCT (Carl Zeiss Meditec; software version 6.5) imaged the RNFL with the "optic disc cube" scan, generating an RNFL thickness map (200×200 pixels) in an optic disc region of approximately 6×6 mm^2. Only images with a signal strength ≥6 were included. Images with motion artifact, poor centration, or missing data (e.g., blinking) were checked by the operator and discarded, with re-scanning performed in the same visit. After excluding 11 images with signal strength consistently <6 and 10 eyes with registration failure with the baseline images for progression analysis, 4072 RNFL thickness maps from 4072 follow-up visits among 139 patients (240 eyes) with glaucoma were available for RNFL change analysis. The RNFL measurements obtained with the Cirrus HD-OCT have been shown to have low test–retest variability.[10,15,16]

Guided Progression Analysis

The Cirrus HD-OCT GPA (Carl Zeiss Meditec) evaluated progressive RNFL thinning of the RNFL thickness map in 50×50 superpixels (1 superpixel = 4×4 pixels) using an event-based analysis. The GPA aligned, registered, and compared the baseline and follow-up RNFL thickness maps in individual superpixel locations. A superpixel would be encoded in yellow in the RNFL thickness change map when the differences in RNFL thickness between the follow-up and the first and second baseline images were greater than the test–retest variability of a superpixel location, and in red if the differences were evident in a consecutive follow-up image. In this study, progressive RNFL thinning was defined when at least 20 contiguous superpixels (factory default) encoded in red in the RNFL thickness change map were detected during the study follow-up and the same changes were observed in the latest follow-up visit (Fig 1A).

Trend-based Progression Analysis

The same 4072 RNFL thickness maps analyzed by GPA were exported to a computer for TPA, which is a trend-based algorithm custom-designed in MATLAB (The MathWorks, Inc., Natick, MA), to determine the rate of change of RNFL thickness in individual superpixels of the RNFL thickness map.[17] After aligning and registering the longitudinal image series (similar to GPA), linear regression analysis between RNFL thickness and follow-up time was performed at individual superpixels of the