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Rates of Retinal Nerve Fiber Layer Loss in Contralateral Eyes of Glaucoma Patients with Unilateral Progression by Conventional Methods

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Purpose: To determine whether progressive retinal nerve fiber layer (RNFL) loss occurs in the contralateral eye of patients with glaucoma showing unilateral progression according to conventional diagnostic methods.

Design: Prospective, longitudinal, observational cohort study.

Participants: Three hundred forty-six eyes of 173 patients (118 eyes with glaucoma and 228 eyes with suspect glaucoma at baseline) followed up for an average of 3.5±0.7 years.

Methods: All subjects underwent standard automated perimetry (SAP; Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) and spectral-domain (SD) optical coherence tomography (OCT; Spectralis; Heidelberg Engineering, Inc., Carlsbad, CA) in both eyes at 6-month intervals. Eyes were determined as progressing by conventional methods if there was progression on masked grading of optic disc stereophotographs or SAP Guided Progression Analysis (GPA; Carl Zeiss Meditec; "likely progression"). Rates of change in SD OCT average RNFL thickness were obtained using a linear mixed effects model. Rate of global loss was calculated using a random coefficient model and compared for nonprogressing patients, progressing eyes, and fellow eyes of unilateral progressing patients.

Main Outcomes Measures: Rate of change in global RNFL thickness.

Results: Thirty-nine subjects showed evidence of unilateral progression by GPA, disc photographs, or both during follow-up. Mean ± standard error rate of RNFL loss in eyes progressing by conventional methods was −0.89±0.22 μm/year ($P < 0.001$). The contralateral eyes of these subjects also showed significant loss of RNFL over time (−1.00±0.20 μm/year; $P < 0.001$). One hundred thirty-four subjects did not show progression by conventional methods in either eye. These eyes also showed a significant decline over time in average RNFL thickness (−0.71±0.09 μm/year; $P < 0.001$); however, the rate of change in these eyes was slower than that of the contralateral eye of patients showing unilateral progression ($P < 0.001$).

Conclusions: Loss of RNFL thickness was seen in a substantial number of contralateral eyes of glaucoma patients showing unilateral progression by conventional methods. These findings indicate that assessment of RNFL thickness by SD OCT may show progressive glaucomatous damage that is not detected by visual fields or optic disc stereophotography. *Ophthalmology 2015;122:2243-2251 © 2015 by the American Academy of Ophthalmology.*

Detection of progression is the cornerstone of management of patients with glaucoma. Assessment of progression relies on establishing accurate baseline measurements and monitoring for change over time.[1] In clinical practice, progressive visual field loss generally has been evaluated using standard automated perimetry (SAP). Although there is currently no consensus regarding the best method for detecting progressive field loss on SAP, tools such as Guided Progression Analysis (GPA; Carl Zeiss Meditec, Dublin, CA) have been used widely in clinical practice to assist in management and treatment decisions.[2–4]

Despite SAP being the most commonly used method to assess progression, the results of several longitudinal investigations have provided evidence that many patients may show progressive structural damage in the absence of detectable visual field losses on SAP. Clinical trials such as the Ocular Hypertension Treatment Study have used serial assessment of optic disc stereophotographs to detect progressive damage from glaucoma.[5] However, interpretation of optic disc stereophotographs is subjective, and this method may be relatively insensitive to detecting certain patterns of progression, such as diffuse retinal nerve fiber layer (RNFL) loss.[6] Therefore, it is conceivable that progression may occur in some patients, despite going largely undetected by conventional tests such as SAP GPA and optic disc stereophotography.

Over the past decade, several longitudinal investigations have validated the use of imaging technologies for detection

http://dx.doi.org/10.1016/j.ophtha.2015.07.027
ISSN 0161-6420/15

of progressive structural damage in glaucoma.[7–10] Assessment of RNFL using spectral-domain (SD) optical coherence tomography (OCT) can provide objective and reproducible measurements of RNFL thickness and quantify rates of structural deterioration in glaucoma. Rates of RNFL thinning as measured by OCT have been shown to be predictive of future functional losses in the disease and to be related to measures of quality of life.[11–14]

Although glaucoma typically is a bilateral disease, unilateral progression may be seen often in clinical practice. However, it is conceivable that assessment of progression with more sensitive methods actually may reveal deterioration to occur in those eyes that do not show progression when measured by conventional methods. Despite the increasing use of OCT in clinical practice, to the best of our knowledge, there have been no reports evaluating the ability of this technology to detect progression in the fellow eyes of patients who show only unilateral progression by conventional assessment with SAP or optic disc photographs. This is an important topic because, arguably, undetected progression in the better eye may be of greater significance for a patient's quality of life than progression in the worse eye.[14,15] The purpose of this study was to determine whether progressive RNFL loss occurs in the contralateral eye of patients with glaucoma showing unilateral progression according to conventional diagnostic methods and to compare rates of change in these eyes.

Methods

Patients

This was a longitudinal observational cohort study involving 346 eyes of 173 participants from the Diagnostic Innovations in Glaucoma Study, a prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma. The study was conducted at the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California, San Diego. Methodologic details have been described previously.[16] Written informed consent was obtained from all participants, and the institutional review board and human subjects committee at University of California, San Diego, prospectively approved all protocols and methods, which adhered to the Declaration of Helsinki. The study was also conducted in accordance with the regulations of the Health Insurance Portability and Accountability Act.

At each visit during follow-up, patients underwent a comprehensive ophthalmologic examination, including review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy, dilated funduscopic examination with 78-diopter (D) lens, stereoscopic optic disc photography (Kowa WX3D; Kowa OptiMed, Torrance, CA), Spectralis SD OCT (software version 5.4.7.0; Heidelberg Engineering, Inc., Carlsbad, CA), and SAP (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) using the Swedish interactive threshold algorithm standard 24-2. Only patients with open angles on gonioscopy were included. Subjects were excluded if they had visual acuity less than 20/40, spherical refraction outside ±5.0 D, cylinder correction outside ±3.0 D, a combination thereof, or any other ocular or systemic disease that could affect the optic nerve or the visual field.

The study included patients diagnosed with glaucoma, as well as those suspected of having the disease, both of whom were determined at baseline visit. Patients were diagnosed with glaucoma if either eye had repeatable (≥3 consecutive) abnormal SAP results, defined as pattern standard deviation outside 95% normal confidence limits, or glaucoma hemifield test results outside normal limits. Glaucoma suspects were diagnosed if they had a history of elevated IOP (>21 mmHg), suspicious or glaucomatous appearance of the optic nerve, or both, but normal and reliable visual field results.

For the purposes of the analysis, subjects with both eyes eligible from the Diagnostic Innovations in Glaucoma Study were included and those with only 1 eye eligible were excluded. To be included in the analysis, each patient was required to have undergone at least 5 SAP tests and 5 SD OCT tests over a duration of at least 1 year of follow-up. The images of RNFL with Spectralis and visual field tests with SAP using the Swedish interactive threshold algorithm standard 24-2 were obtained at 6-month intervals during follow-up. The study included a total of 2646 Spectralis visits, with an average of 752 visits per year.

Stereophotographs

All patients underwent stereoscopic optic disc photography repeated at least every 12 months during follow-up. The images were reviewed with a stereoscopic viewer (Screen-VU stereoscope; PS Manufacturing, Portland, OR) by 2 or more experienced graders masked to the subjects' identity and any other test results. Details of the methodology used to grade the optic disc photographs at University of California, San Diego, Optic Disc Reading Center have been described elsewhere.[16,17] Discrepancies between the 2 graders were resolved by consensus or adjudication by a third experienced grader. Only photographs with adequate quality were used.

Progression assessment was based on focal or diffuse thinning of the neuroretinal rim, or both; increased excavation; and appearance or enlargement of RNFL defects. Change in rim color, presence of disc hemorrhage, or progressive parapapillary atrophy was not sufficient for characterization of progression.

Optical Coherence Tomography

Spectralis SD OCT was used to measure global RNFL in this study. Details of the operation have been described previously.[18,19] All images were reviewed by experienced technicians at the Imaging Data Evaluation and Assessment Center. To be included, images had to be centered, with accurate segmentation, and to have a signal strength of more than 15 dB. For this study, we used the global RNFL thickness, which corresponds to the average RNFL thickness in the 3.4-mm-diameter peripapillary circle around the optic nerve head. This parameter has been shown to perform well in the assessment of rates of change in previous studies.[17,20]

Standard Automated Perimetry

All visual field results were reviewed by 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. Glaucomatous visual field progression was evaluated by Humphrey Field Analyzer GPA software. For each individual point on the visual field, GPA compares the sensitivity of a follow-up test with the one from averaging 2 baseline visits at the same location. It flags points whose changes demonstrate more than expected variability (at 95% significance level). If significant change is detected in more than 3 points and is repeated at the same location in 2 consecutive follow-up tests, GPA flags the last test as "possible progression." If more than 3 points have significant changes detected and repeated in 3 consecutive follow-ups at the same location, GPA flags the last