AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Rates of Local Retinal Nerve Fiber Layer Thinning before and after Disc Hemorrhage in Glaucoma

Tadamichi Akagi, MD, PhD,[1,2] *Linda M. Zangwill, PhD,*[1] *Luke J. Saunders, PhD,*[1] *Adeleh Yarmohammadi, MD,*[1] *Patricia Isabel C. Manalastas, MD,*[1] *Min Hee Suh, MD,*[1,3] *Christopher A. Girkin, MD, MSPH,*[4] *Jeffrey M. Liebmann, MD,*[5] *Robert N. Weinreb, MD*[1]

Purpose: To investigate longitudinal temporal and spatial associations between disc hemorrhage (DH) and rates of local retinal nerve fiber layer (RNFL) thinning before and after DHs.

Design: Longitudinal, observational cohort study.

Participants: Forty eyes of 37 participants (23 with glaucoma and 17 with suspect glaucoma at baseline) with DH episodes during follow-up from the Diagnostic Innovations in Glaucoma Study and the African Descent and Glaucoma Evaluation Study.

Methods: All subjects underwent optic disc photography annually and spectral-domain optical coherence tomography (OCT) RNFL thickness measurements every 6 months. The rates of RNFL thinning were calculated using multivariate linear mixed-effects models before and after DH.

Main Outcome Measures: Rates of global and local RNFL thinning.

Results: Thirty-six eyes of 33 participants with inferior or superior DHs were analyzed. The rates of RNFL thinning were significantly faster in DH quadrants than in non-DH quadrants after DH (−2.25 and −0.69 μm/year; $P < 0.001$). In the 18 eyes with intensified treatment after DH, the mean rate of RNFL thinning significantly slowed after treatment compared with before treatment in the non-DH quadrants (−2.89 and −0.31 μm/year; $P < 0.001$), but not in the DH quadrants (−2.64 and −2.12 μm/year; $P = 0.19$). In 18 eyes with unchanged treatment, the rate of RNFL thinning in the DH quadrant was faster after DH than before DH ($P = 0.008$). Moreover, compared with eyes without a treatment change, intensification of glaucoma treatment after DH significantly reduced the global, non-DH quadrants, and DH quadrant rates of RNFL thinning after DH compared with before DH (global, $P = 0.004$; non-DH quadrant, $P < 0.001$; DH quadrant, $P = 0.005$). In the multiple linear regression analysis, treatment intensification (β, 1.007; $P = 0.005$), visual field mean deviation (β, 0.066; $P = 0.049$), and difference in intraocular pressure before and after DH (β, −0.176; $P = 0.034$) were associated significantly with the difference of global RNFL slope values before and after DH.

Conclusions: Although the rate of RNFL thinning worsened in a DH quadrant after DH, glaucoma treatment intensification may have a beneficial effect in reducing this rate of thinning. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

Glaucoma is characterized by progressive loss of retinal ganglion cells and associated morphologic changes to the optic nerve and retinal nerve fiber layer (RNFL).[1] Disc hemorrhage (DH) is well known as an important risk factor for the development and progression of glaucoma.[2–6] Previous studies have shown the association between DH and glaucoma progression in function[4–6] and structure.[7–11] The location of DH also is known to relate spatially to notches in the neuroretinal rim,[12] progressive localized thinning of the RNFL,[13] and focal visual field progression.[2,5,14,15] However, there has been less detailed information regarding the longitudinal temporal and spatial association between DH and glaucoma progression.

It has been reported previously that DH might be a result of progressive structural damage using visual field testing[5] or optic disc photographs.[10] However, it has not been clarified whether DH is only consequent to glaucoma progression or whether it could accelerate subsequent glaucoma progression. The ability to image the RNFL quantitatively provides an opportunity to investigate this.

Recent spectral-domain (SD) optical coherence tomography (OCT) technology enables detection of local progressive RNFL thinning with high sensitivity and reproducibility.[16–18] Longitudinal reports have evaluated glaucoma progression retrospectively after DH using time-domain OCT or SD OCT, but not before DH.[7–9] It has been observed that the progressive RNFL thinning after DH was associated with the location of DH compared with the respective contralateral quadrants or the contralateral eyes without DH. However, the relationship between structural damage and subsequent DH still is not well understood.

http://dx.doi.org/10.1016/j.ophtha.2017.03.059
ISSN 0161-6420/17

Disc hemorrhage often is used as an indicator for additional intraocular pressure (IOP) lowering, and Medeiros et al[6] previously showed that IOP lowering was associated with the reduction of the rate of visual field progression after DH. Their results suggest that the influence of glaucoma treatments on glaucoma progression should be considered in investigating glaucoma progression related to DH. In this study, we investigated the differences in rates of local RNFL thinning before and after DH and the influence of glaucoma treatment after DH on these rates.

Methods

Participants

Participants were enrolled in the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES). The DIGS is conducted at the Hamilton Glaucoma Center at the University of California, San Diego (UCSD), and ADAGES is a multicenter study conducted at the UCSD, University of Alabama at Birmingham, and New York Eye and Ear Infirmary. The protocols of the 2 studies are identical, and the methodological details have been described.[19]

All patients from the DIGS and ADAGES who met the following inclusion criteria were enrolled in the present study. Informed consent was obtained from all participants. This prospectively designed study received institutional review board approval at each of the involved sites. The methodology adhered to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act.

Eligible participants had best-corrected visual acuity of 20/40 or better, spherical refraction within ±5.0 diopters, cylinder correction within ±3.0 diopters, and open angles on gonioscopy at study entry. Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract or glaucoma surgery). Eyes with coexisting retinal disease, uveitis, or nonglaucomatous optic neuropathy were excluded from the investigation. Normal participants were excluded from this study. All participants who had at least 1 DH during follow-up and underwent at least 2 OCT examinations of sufficient quality both before and after the DH were analyzed in the current study. Eyes that did not have target DHs located in the inferior or superior quadrant were excluded from the analysis. When the eye had multiple DHs during OCT follow-up, the first DH during the OCT follow-up period was determined as the target DH. If any additional DHs were observed in the contralateral quadrant of the target DH during OCT follow-up periods, the eye was excluded from the analysis.

Stereophotography

All patients had stereoscopic optic disc photographs 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 to other test results. The location of the DH was classified into four 90-degree sectors (superior, inferior, temporal, and nasal). The methodology used to grade optic disc photographs at the UCSD Optic Disc Reading Center has been provided by Sample et al.[19] Only photographs of adequate quality were included. Discrepancies between the 2 graders were resolved by consensus or adjudication by a third experienced grader. For this report, DHs were defined as located within 1/2 disc diameter from the optic disc border or within the RNFL as a splinter or flame-shaped hemorrhage and not associated with optic disc edema, papillitis, diabetic retinopathy, central or branch retinal vein occlusion, or any other retinal disease.[20]

Spectralis Spectral-Domain Optical Coherence Tomography

The RNFL thickness was measured with the Spectralis SD OCT parapapillary circle scan (software version 5.4.7.0; Heidelberg Engineering, Heidelberg, Germany). Details of the procedure have been described.[17,21] Spectralis incorporates a real-time eye tracking system that couples a 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. A total of 1536 A-scan points were acquired from a 3.45-mm circle centered on the optic disc. Spectralis SD OCT images measured from April 2009 to August 2016 were included, and the RNFL thickness measurements were estimated in 4 sectors separated into 90-degree intervals (superior, inferior, temporal, and nasal) using the same criteria as DH on photographs. All images were processed and reviewed by the Imaging Data Evaluation and Assessment Center at the UCSD. Images with noncentered scans, inaccurate segmentation of the RNFL, or signal strength of 15 decibels or less were excluded from the analysis.

Standard Automated Perimetry

All standard automated perimetry was performed using the 24-2 Swedish interactive threshold algorithm (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) strategies. Only repeatable and reliable tests (≤33% fixation losses and false-negative results and ≤15% false-positive results) were included.

Statistical Analysis

The rates of global or local RNFL thinning before and after DH were compared globally or sectorally. Linear mixed-effects modeling was used to estimate the rates of change of global or local RNFL thinning to account for repeated measurements over time and correlations between the 2 eyes of an individual.[17,18,22] A set of mixed-effects models were fit with RNFL thickness as the response, time as a fixed effect, and random intercept and slope for each eye nested within each patient. The random slope values calculated using mixed-effects modeling were compared with the paired *t* test between before and after DHs. We fitted models to evaluate rates of loss in global RNFL, in DH quadrants and non-DH quadrants separately. Comparisons between these groups for categoric variables were evaluated using the chi-square test. Univariate linear regression analysis and stepwise multiple linear regression analysis were performed to identify parameters associated with differences in global RNFL slope values before and after DH. All statistical analyses were performed with R version 3.3.1 (http://www.r-project.org) and SPSS version 20 (IBM Corp., Armonk, NY). The mixed-effects modeling was performed using "lme4" in the R package. *P* values <0.05 were considered statistically significant.

Results

In 40 eyes of 37 subjects, at least 1 DH was detected in optic disc stereophotographs of the subjects during OCT follow-up. Table 1 shows the demographic and ophthalmic characteristics of the study participants. Four eyes of 4 subjects were excluded from the analysis because the location of their target DHs was not inferior or superior. As a result, a total of 36 eyes of 33 participants were analyzed in this study. Seven eyes (19%) of 7