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Association between Rates of Retinal Nerve Fiber Layer Thinning and Previous Disc Hemorrhage in Glaucoma

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Purpose: To investigate the relationship between previous disc hemorrhage (DH) and subsequent rates of retinal nerve fiber layer (RNFL) thinning.

Design: Longitudinal, observational cohort study.

Participants: Twenty-eight patients with glaucoma and patients with suspected glaucoma who had a history of DH in 1 eye (unilateral DH), but not in the fellow eye, enrolled in the Diagnostic Innovations in Glaucoma Study and the African Descent and Glaucoma Evaluation Study were included.

Methods: All subjects underwent annual optic disc photography and semiannual spectral-domain OCT RNFL thickness measurements. Multivariable linear mixed-effects models were used to investigate the relationship between the presence of previous DH and RNFL thinning rates while adjusting for potential confounding factors, such as race, age, mean intraocular pressure (IOP), baseline disease severity, and central corneal thickness (CCT). The relationship between the timing of DH and the rates of RNFL thinning also was investigated in eyes with a history of DH.

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

Results: Previous DH was significantly associated with faster RNFL thinning rates globally (−0.39 μm/year faster, $P = 0.010$), in DH quadrants (−0.77 μm/year faster, $P = 0.012$), and non-DH quadrants (−0.49 μm/year faster, $P = 0.038$) after adjustment for race, mean IOP, baseline age, baseline standard automated perimetry mean deviation, and CCT. Higher IOP was also significantly associated with faster thinning rates globally (−0.07 μm/year faster per 1 mmHg higher, $P = 0.047$) and in DH quadrants (−0.10 μm/year faster per 1 mmHg higher, $P = 0.044$). In eyes with a history of DH, the time elapsed from the latest DH episode to the first OCT examination was not significantly associated with the rate of RNFL thinning.

Conclusions: A history of DH is an independent risk factor for faster rates of RNFL thinning in non-DH quadrants and in DH quadrants; this risk is present even in eyes that exhibited DH several years earlier. *Ophthalmology Glaucoma 2018;1:23-31 © 2018 by the American Academy of Ophthalmology*

Disc hemorrhage (DH) is an important risk factor for the development and progression of glaucoma and is significantly associated with glaucomatous visual field and optic disc progression.[1-16] Progressive glaucomatous changes in the retinal nerve fiber layer (RNFL) have been identified within optic disc photographs and red-free fundus photographs, as well as on time-domain OCT[9-14] and spectral-domain (SD) OCT.[17-20] We recently reported that DH often precedes rapid RNFL thinning in the DH quadrant; moreover, more aggressive treatment can slow thinning of the RNFL.[21] This accelerated RNFL thinning at least partly explains glaucoma progression in eyes with DH. Of note, SD OCT studies have shown that RNFL thinning after DH occurs more rapidly within the DH quadrant than in the corresponding quadrant of the contralateral eye.[15,16] However, it is not clear whether a history of DH even when it occurred several years earlier is still a risk factor for glaucoma progression or whether the duration of elapsed time since DH affects subsequent RNFL thinning.

The purpose of this study was to characterize the relationship between previous occurrences of DH and the rates of RNFL thinning (global and local) in glaucomatous eyes.

Methods

Participants

Participants were recruited from the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES). The DIGS is a longitudinal study conducted at the Hamilton Glaucoma Center at the University of California, San Diego (UCSD), and the ADAGES is a multicenter study conducted at UCSD, the University of Alabama at Birmingham, and the New York Eye and Ear Infirmary. The protocols

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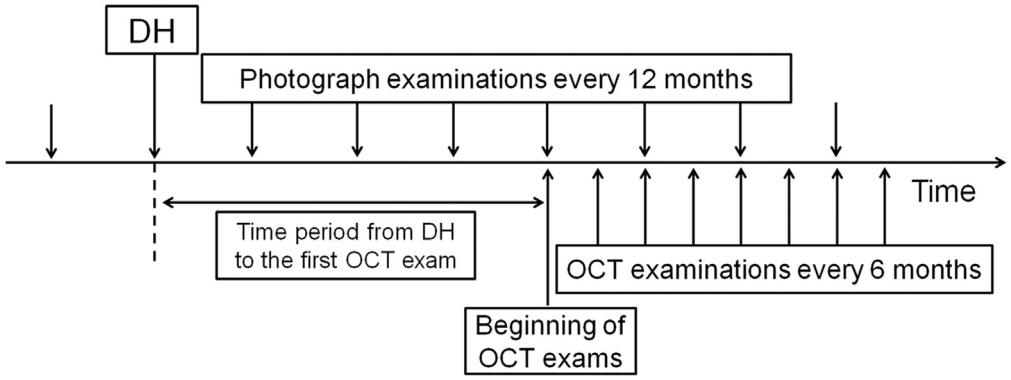

Figure 1. Schematic diagram showing examination protocols of this study. This study included only patients with unilateral disc hemorrhage (DH) that occurred before OCT follow-up. The time period from the latest episode of DH to the first OCT examination was evaluated.

of the 2 studies for the data included in this report are identical, and the methodological details have been described.[22]

This prospective study obtained 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. Informed consent was obtained from all participants.

All DIGS and ADAGES patients who met the inclusion criteria described were enrolled in the present study. Eligible participants exhibited baseline best-corrected visual acuities of 20/40 or better, spherical refraction within the range of ±5.0 diopters, cylinder correction within the range of ±3.0 diopters, and open angles on gonioscopy at study entry. Participants were excluded if they reported a history of intraocular surgery (with exceptions made for uncomplicated cataract or glaucoma surgery). Patients who exhibited coexisting retinal disease, uveitis, or nonglaucomatous optic neuropathy were excluded from the investigation.

The study included patients with glaucoma and patients with suspected glaucoma. Eyes were classified as glaucomatous if they had 2 or more repeatable glaucomatous visual field defects at baseline, defined as a pattern standard deviation with $P < 0.05$, or glaucoma hemifield test results outside normal limits. Eyes were classified as glaucoma suspects if they had a history of elevated intraocular pressure (IOP) (>21 mmHg), suspicious or glaucomatous appearance of the optic nerve but normal and reliable visual field results at baseline, or both. Participants were included if they had experienced at least 1 unilateral DH before the OCT follow-up period and had also completed at least 3 high-quality OCT examinations with ≥2 years of follow-up. We have reported that RNFL thinning rates are generally faster immediately after the occurrence of a DH.[21] In this article, we have focused on the longer-term effect of the occurrence of past DH on RNFL thinning. For these reasons, subjects were excluded when DHs were detected after the initiation of OCT follow-up. If fellow eyes (i.e., those without a history of DH) of the study participants had not been followed by OCT for ≥2 years (including at least 3 OCT examinations), those subjects were excluded from the current study.

Stereophotography

All patients underwent stereoscopic optic disc photography every 12 months during follow-up (Fig 1). The images were reviewed with a stereoscopic viewer (Screen-VU stereoscope; PS Manufacturing, Portland, OR) by ≥2 experienced graders who were masked to the subjects' identity and any additional test results. The methodology used at the UCSD Optic Disc Reading Center to grade optic disc photographs for quality and glaucomatous optic neuropathy has been described.[22] Only photographs of good quality were included in this analysis. Discrepancies between the 2 graders were resolved by consensus or by adjudication with a third experienced grader. For this report, DHs were defined as those hemorrhages located within one half disc diameter from the optic disc border or within the RNFL as a splinter or flame-shaped hemorrhage; they were not associated with optic disc edema, papillitis, diabetic retinopathy, central or branch retinal vein occlusion, or any other retinal disease.[23,24] Relative location of the DHs was classified into four 90-degree sectors (superior, inferior, temporal, and nasal).[21]

In eyes that exhibited superior or inferior target DHs, the quadrants where DHs were located were defined as DH quadrants, whereas contralateral quadrants were defined as non-DH quadrants.[21] In the fellow eyes that did not exhibit DH, DH and non-DH quadrants were defined relative to their classification in the eye with DH. For example, in fellow eyes that were contralateral to eyes with superior DH, superior quadrants were defined as DH quadrants and inferior quadrants were defined as non-DH quadrants, following the same manner as in the eyes with superior DH.

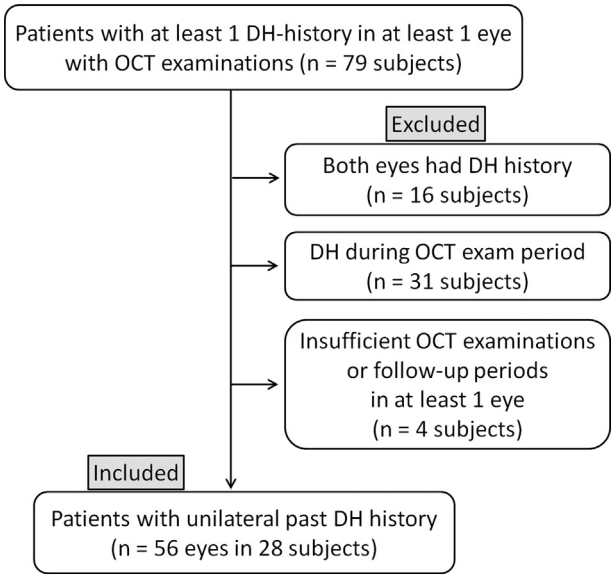

Figure 2. Flowchart depicting the selection of subjects for the study. DH = disc hemorrhage.