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Choroidal Microvasculature Dropout Is Associated with Progressive Retinal Nerve Fiber Layer Thinning in Glaucoma with Disc Hemorrhage

Hae-Young Lopilly Park, MD, PhD, Jin Woo Kim, MD, Chan Kee Park, MD, PhD

Objective: We used OCT angiography (OCT-A) to investigate parapapillary choroidal microvasculature dropout (MvD) in glaucomatous eyes with or without disc hemorrhage (DH), and the association with changes in retinal nerve fiber layer (RNFL) thickness.

Design: An observational case-control study.

Participants: Eighty-two open-angle glaucoma (OAG) eyes with DH and 68 OAG eyes without DH that underwent at least 4 serial OCT examinations were included.

Methods: MvD was defined as complete loss of microvasculature within the choroidal layer of the parapapillary region, as revealed by standardized assessment of OCTA-derived density maps of the vessels of the optic nerve head. The circumferential extent of MvD was measured on OCT-A images. The RNFL thinning rate was calculated using a linear mixed model. Kaplan-Meier survival analysis and the log-rank test were used to compare the cumulative risk ratio of progression between groups stratified by DH and MvD.

Main Outcome Measures: MvD detection rate, the extent of MvD as measured by the MvD angle, and RNFL thinning rate.

Results: MvD was found in 38 (46.3%) eyes with DH at the prior DH site, which was found in only 20 (29.4%) eyes without DH, which was significantly different between the 2 groups ($P = 0.025$). Patients with progressive glaucoma exhibited significantly more MvD than the stable patients in both DH and no-DH groups. There were statistically significant differences between groups subdivided by the presence of DH and MvD as assessed by Kaplan-Meier analysis (log-rank test, $P < 0.001$). The angle of MvD was significantly greater in eyes with recurrent DH compared with eyes with single DH. Presence of DH, recurrent DH, and presence of MvD were factors associated with progressive RNFL thinning.

Conclusions: We found that MvD was frequent in progressive OAG eyes on the choroidal map of OCT-A, which was more frequently found at the prior DH locations in eyes with DH. This means that observing the presence of MvD using OCT-A may provide a biomarker for glaucoma progression, especially in eyes with DH. *Ophthalmology 2018;■:1–11 © 2018 by the American Academy of Ophthalmology*

Disc hemorrhage (DH) is a significant risk factor for glaucoma development and progression.[1–3] The Ocular Hypertension Treatment Study found that DH was a risk factor for glaucoma development in ocular hypertensive eyes.[3] The Early Manifest Glaucoma Trial and Collaborative Normal-Tension Glaucoma Study showed that DH was significantly associated with glaucoma progression.[1,4] However, little is known about the underlying pathogenic mechanism. Also, it remains unclear as to which features of DH may have prognostic implications.

Fluorescein angiography, laser Doppler flowmetry, and laser speckle flowgraphy have revealed that the extent of defects in optic disc filling was more prevalent, and that disc leaks and delayed choroidal filling, especially parapapillary choroidal filling delay, were more common in glaucomatous eyes than in normal eyes.[5–9] Few reports have specifically investigated changes in glaucomatous eyes with DH. Previously, we used disc angiography to identify vessel-filling defects, and delayed filling, of vessels of the optic nerve head (ONH) in glaucomatous eyes with DH.[10] However, the relationship between microvascular changes and glaucoma progression in eyes with DH has not yet been described. OCT angiography (OCT-A) yields both qualitative and quantitative microvascular data, and allows evaluation of the perfusion status of the various retinal layers. Specifically, OCT-A images of the deep parapapillary layer have recently revealed regional microvasculature dropout (MvD) in glaucomatous eyes.[11–13] MvD in the parapapillary choroidal layer around the ONH was regionally associated with retinal nerve fiber layer (RNFL) defects in glaucomatous eyes, suggesting that microvascular changes may affect glaucoma pathogenesis. In the present study, we used OCT-A to evaluate microvascular perfusion in the ONH region of glaucomatous eyes with and without

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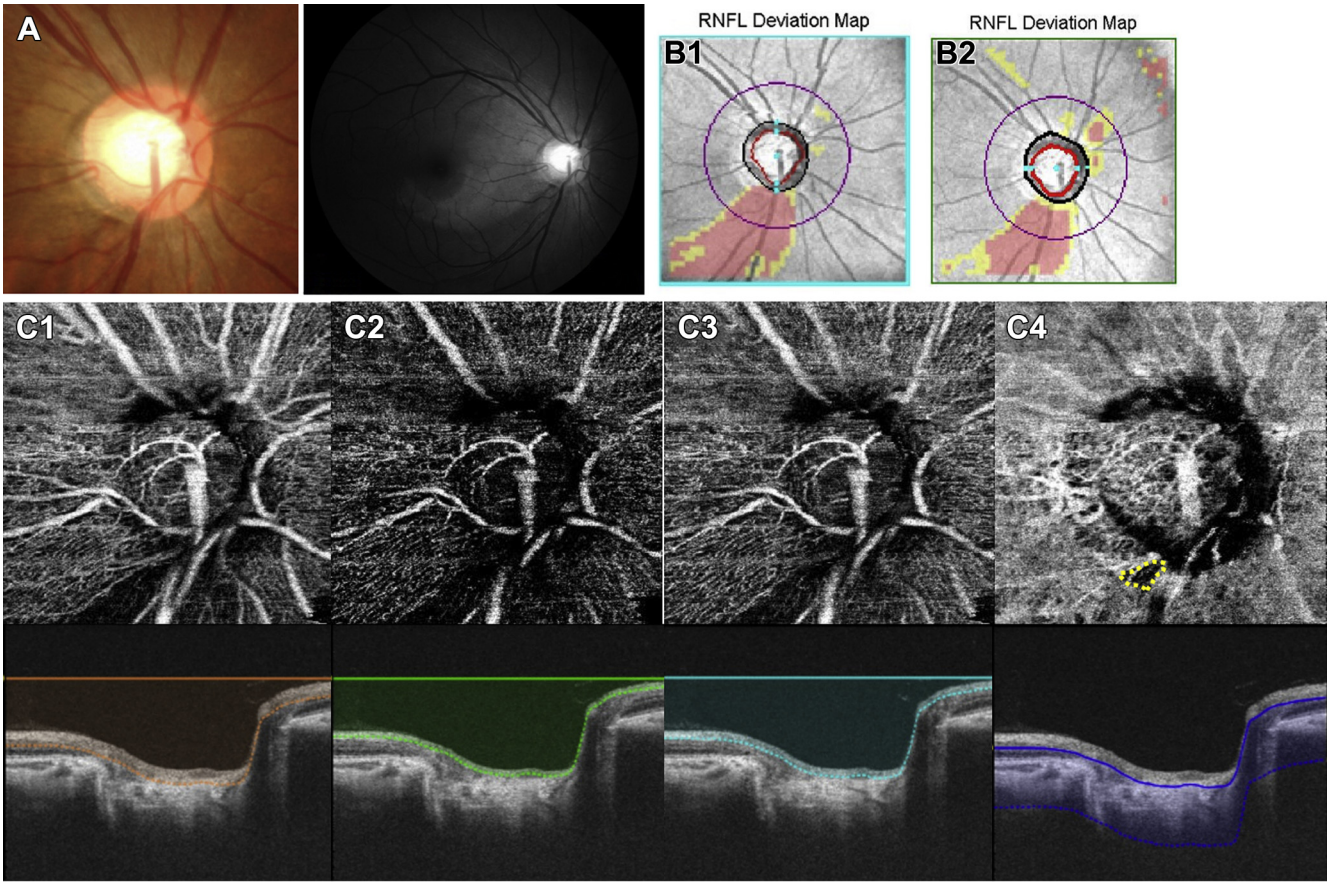

Figure 1. A representative case. **A,** A 48-year-old man with open-angle glaucoma had a localized inferotemporal retinal nerve fiber layer (RNFL) defect without disc hemorrhage (DH) during the 5 years of follow-up. **B,** This patient did not show progressive RNFL thinning during the follow-up period (B-1, baseline; B-2, end of follow-up). **C,** OCT angiography generates en face images via automated layer segmentation around the optic nerve head into 4 layers. The superficial layer (C-1), vitreoretinal layer (C-2), and layer of the radial capillary network (C-3) show capillary loss corresponding to the inferotemporal localized RNFL defect. The parapapillary choroidal microvasculature captures signals from the retinal pigment epithelium that extended to the outer border of the sclera, which mainly includes the signals from the choroid (C-4). A microvasculature dropout is observed in the inferotemporal region corresponding to, but smaller than, the RNFL defect.

DH, and explored the clinical significance of regional MvD at the site of prior DH in terms of progressive RNFL thinning.

Methods

Subjects

This study was a component of the Catholic Medical Center Glaucoma Progression Study (CMC-GPS), which commenced in 2009 at Seoul St. Mary's Hospital, Seoul, South Korea. The work was approved by our institutional review board of Seoul St. Mary's Hospital and we followed all relevant tenets of the Declaration of Helsinki. We enrolled all consecutive eligible patients who were willing to participate, and all gave written informed consent.

All open-angle glaucoma (OAG) patients enrolled in the CMC-GPS underwent a complete ophthalmic examination, including a review of medical history, measurement of best-corrected visual acuity, refraction assessment, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, measurement of central corneal thickness via ultrasound pachymetry (Tomey Corp, Nagoya, Japan), measurement of axial length with ocular biometry (IOLMaster; Carl Zeiss Meditec, Dublin, CA), dilated stereoscopic examination of the optic disc, red-free fundus photography (Canon, Tokyo, Japan), Cirrus OCT (Carl Zeiss Meditec), and Humphrey visual field (VF) examination using the Swedish interactive threshold Standard 24-2 algorithm (Carl Zeiss Meditec).

All patients were followed up every 1−3 months with color disc and fundus photography. VF and OCT examinations were performed at intervals of 6 months during the first 3 years after the diagnosis of glaucoma, and every year thereafter.

Data from the CMC-GPS were reviewed by 2 of the authors (H.Y.P. and J.W.K.). OAG patients with DH who had been followed up for at least 2 years after DH documentation, and who had undergone at least 4 serial OCT examinations, were evaluated in the present study. The comparison group included OAG patients without DH during the entire follow-up period (at least 4 years) who had undergone at least 4 serial OCT examinations. All such patients underwent additional OCT-A (DRI OCT Triton; Topcon, Tokyo, Japan) examinations. OAG was defined by the presence of a glaucomatous optic disc (exhibiting diffuse or localized rim thinning, a notch in the rim, or a vertical cup-to-disc ratio $\geq$0.2 compared with the other eye); a VF finding consistent with glaucoma (a cluster of $\geq$3 non-edge points on the pattern deviation plot with a probability