Clinical Significance of Recurrent Disc Hemorrhage and Choroidal Microvasculature Dropout on Optical Coherence Tomography Angiography in Glaucoma

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Purpose. The purpose of this study was to investigate the clinical significance of recurrent disc hemorrhage (DH) and choroidal microvasculature dropout (MvD).

Methods. A retrospective cohort study was conducted of 181 eyes with open-angle glaucoma. The clinical characteristics of patients with nonrecurrent and recurrent DH with and without MvD were investigated.

Results. Fifty-eight patients (32.0%) had a single, nonrecurrent DH, and 63 (34.8%) had more than one DH. Sixty eyes (33.1%) with no history of DH were presented as a control group. MvD was more frequent in the recurrent DH group (44.4%) than in the nonrecurrent DH group (27.6%, $P = 0.041$). The recurrent DH with MvD group experienced more frequent central visual field (VF) progression (71.4%) than the recurrent DH without MvD group (17.1 %, $P < 0.001$). The recurrent DH without MvD group had a higher frequency of DH recurrence at different locations (42.9%) and more vascular symptoms (37.1%) than the recurrent DH with MvD group (14.3% and 7.1%, $P = 0.013$ and $P = 0.005$, respectively). Presence of DH, presence of MvD, vascular symptoms, and DH recurrence at different locations were the factors associated with central VF progression in multivariate analysis.

Conclusions. DH occurrence and the presence of MvDs constitute critical parameters associated with central VF progression. In the presence of MvD, recurrent DH was more likely to recur at the same location as the MvD, whereas recurrent DH without MvD was related to vascular symptoms and recurred at other locations. When eyes present with recurrent DH and MvD, closer follow-up and more aggressive treatment are required to prevent the progression of central VF.

Keywords: disc hemorrhage (DH), choroidal microvasculature dropout (MvD), optical coherence tomography angiography (OCT-A)

Glaucoma is a complex and progressive optic neuropathy involving the loss of retinal ganglion cells (RGCs), a leading cause of irreversible blindness worldwide. Despite significant advancements in understanding glaucoma, the intricate interplay between structural and vascular components in glaucoma pathogenesis continues to pose challenges. The mechanical and vascular theories are two major perspectives used to explain the pathogenesis of glaucoma.[1–3] The mechanical theory focuses on the structural changes of the posterior eye structures, caused by elevated intraocular pressure (IOP). Elevated IOP can lead to mechanical stress on the lamina cribrosa of the optic nerve head (ONH), the region known to be particularly susceptible to pressure-related damage.[4,5] IOP, a major causative factor that mechanically facilitates glaucoma, can be modified to delay the progression of glaucoma.[6,7] However, some glaucoma cases progress even with sufficient IOP lowering. The vascular theory suggests that chronic hypoxia, vasospasm, vascular dysregulation, or ischemia contribute to the onset of glaucoma, and unstable ocular blood flow and hemodynamic alterations are vascular factors that may contribute to glaucoma progression.[8–10]

Disc hemorrhage (DH) and microvasculature dropout (MvD) on optical coherence tomography angiography (OCT-A) are two important ocular parameters associated with progression of glaucoma[11,12]; interestingly, these parameters display both mechanical and vascular characteristics. DH is associated with structural changes in the lamina cribrosa, optic disc, and retinal nerve fiber layer (RNFL), and is also associated with vascular insufficiency of the ONH.[11,13–16] MvD is a recent finding defined by OCT-A as regional parapapillary vasculature dropout in the choroidal layer.[17,18] Studies have demonstrated an association between myopia and MvD, suggesting that increased mechanical stress on the peripapillary sclera may mechanically compromise the parapapillary microvasculature, resulting in MvD.[18–20] Vascular insufficiency is also thought to contribute to MvD because it is associated with features such as cold extremities, migraines, low ocular perfusion pressure, and central visual field (VF) damage.[21,22] Therefore, the presence of DH and

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MvD is attributed to both mechanical and vascular mechanisms.

The clinical significance of recurrent DH is controversial, as some studies have shown greater RNFL changes[23,24] and VF progression[25] with recurrent DH, whereas recurrent DH was not a significant factor affecting VF progression in others.[26,27] In our previous study,[28] eyes with DHs recurring at different locations were associated with VF progression, whereas DH recurrence at the same location were not. We also suggested that the presence of MvD on OCT-A may predict glaucoma progression in patients with glaucoma with DH.[21] Investigating the link between DHs and MvDs may not only deepen our comprehension of disease mechanisms but also pave the way for more precise diagnostic and therapeutic strategies.

Methods

Participants

This study was a component of the Catholic Medical Center Glaucoma Progression Study (CMC-GPS) and all patients underwent OCT-A (DRI OCT Triton; Topcon, Tokyo, Japan) examinations, which commenced in 2017 at Seoul St. Mary's Hospital, Seoul, South Korea. The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, and all relevant tenets of the Declaration of Helsinki were followed. All consecutive eligible patients who were willing to participate and provided written informed consent were enrolled. Data of patients with open-angle glaucoma (OAG) who developed DH during follow-up were reviewed by two of the authors (H.Y.P. and S.E.O.). Patients with OAG who had been followed up for at least 4 years and had undergone at least 5 serial VF examinations were evaluated in the present study.

All participants enrolled in the CMC-GPS underwent comprehensive ophthalmic examinations, including best-corrected visual acuity, refraction, slit-lamp examination, Goldmann applanation tonometry, gonioscopy, central corneal thickness (UD-800; Tomey Corporation, Japan), axial length (IOLMaster; Carl Zeiss Meditec, Dublin, CA, USA), color and red-free disc/fundus photography (Canon; Tokyo, Japan), Swept-source optical coherence tomography (OCT; DRI OCT Triton; Topcon, Tokyo, Japan), and Humphrey VF examination using Swedish Interactive Threshold Algorithm (SITA) standard 24-2 perimetry (Carl Zeiss Meditec).

Participants underwent detailed history taking and a review of medical/ocular records and prescriptions. Participants were asked whether they had vascular symptoms, defined as a history of migraine, Raynaud's phenomenon, cold extremities, or orthostatic hypotension, as previous study.[29] All patients were followed up every 1 to 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 glaucoma diagnosis and every year thereafter.

OAG was defined as the presence of an open anterior chamber angle confirmed by gonioscopy with a glaucomatous optic disc and compatible glaucomatous VF damage, as reported in previous studies.[29,30] Glaucomatous optic disc appearance was defined as diffuse or localized rim thinning, a notch in the rim, or a vertical cup-to-disc ratio higher than 0.6. Glaucomatous VF damage was defined as: (1) $\geq$3 adjacent points with a probability of $<$5% of the normal population, with one of these points having a probability of $<$1%, (2) glaucoma hemifield test results as outside normal limits, or (3) a pattern standard deviation (PSD) with a P value $<$5% on two VF examinations. The patient was diagnosed with primary open-angle glaucoma (POAG) if the baseline IOP (without topical treatment) was higher than 21 mm Hg and normal tension glaucoma (NTG) if the baseline IOP was 21 mm Hg or lower on repeated measurements on different days.

Additional inclusion criteria were as follows: best-corrected visual acuity $\geq$20/40, VF loss greater than the mean deviation (MD) $>-$12 decibels (dB) at enrollment, and well-controlled disease status with IOP-lowering eye drops. Participants who had undergone surgical or laser treatment, had intraocular or neurological diseases that could lead to VF loss, or were diagnosed with other retinal diseases were excluded. If both eyes of an enrolled patient met all inclusion and exclusion criteria, one eye was randomly chosen for the study.

Definition for DH

Serial disc photographs taken during the entire follow-up period were also evaluated. All DHs that occurred during follow-up were evaluated and recorded based on disc photographs. DH was defined in our previous work,[28] a flame-shaped or splinter-like hemorrhage on the optic disc or peripapillary area extending to the optic disc border. Patients with hemorrhages from all other causes, such as ischemic optic neuropathy, diabetic retinopathy, and retinal vein occlusion, were excluded.

Single or nonrecurrent DH was defined as DH detected only once during the entire follow-up period. Recurrent DH was defined as the occurrence of DH more than once during the follow-up. The DH location was defined as the initial DH location. It was classified as "inferotemporal" when the DH was located within the inferior 60 degrees, 2 clock hours from the vertical line passing the disc center, and "superotemporal" within the 2 clock hours at the superior side from the vertical line, "temporal" within the 2 clock hours at the temporal side of optic disc each hour starting from the horizontal line passing the disc center, and "elsewhere" within the 6 clock hours nasal of the vertical meridian. DH located within the cup base or the peripapillary atrophy region were classified as "elsewhere." Recurrent DH that occurred at different locations compared to the initial DH (outside the initial clock hour) was defined as DH at different locations.

OCT Angiography

The ONH and parapapillary region of 4.5 $\times$ 4.5 mm area was evaluated using a swept-source OCT-A device (DRI OCT Triton; Topcon) with a wavelength of 1050 nm and a scanning speed of 100,000 A-scans per second. Parapapillary choroidal MvD was defined in our previous study,[21] a focal sectoral capillary dropout within the visible microvascular network with a width greater than twofold that of the visible juxtapapillary microvessels on the parapapillary choroidal microvasculature map. Two independent observers (authors H.J.S. and S.E.O.) blinded to the clinical data independently identified all MvDs. Disagreements were resolved by the third author (H.Y.P.). Only clear images with quality scores $>$30 that did not exhibit blurring attributable to motion were analyzed. Additionally, images of DH eyes were thoroughly

reviewed and only eyes with MvD presenting consistently at the same location after the DH has been resolved were considered to have MvD.

Definition of VF Progression

VF progression was determined using linear regression analysis of the MD and PSD values from standard SITA 24-2 VF tests within the follow-up period. The MD and PSD slopes were expressed as changes in decibels per year.

Central progression of VF was defined as a newly detected VF defect on pattern deviation probability map within the 12 points of central 10 degrees, with clusters of 3 or more test point probabilities less than 5%, and 2 or more points with probability less than 1%.

Statistical Analysis

Student *t*-test and the chi-square test were used to compare variables between two groups and post hoc comparison was used to compare variables between three groups. The extent of interobserver agreement in terms of MvD identification was evaluated by calculation of κ coefficients. The MD and PSD of the VF of each patient were subjected to linear regression analysis against time to determine the VF progression rates (dB/year). Univariate and multivariate logistic regression analyses were performed to identify factors associated with central VF progression, recurrent DH and recurrent DH at different locations. Independent variables (*P* values ≤0.10) in the univariate model were included in the multivariate model. A Kaplan-Meier survival analysis and the log rank test were used to compare the cumulative risk ratio of central VF progression between groups divided based on the occurrence of either a single or recurrent DH, and the presence of MvD. First-time central VF progression was regarded as the end point in the survival analysis. The end of follow-up was when the patients without progression were censored. *P* values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS (version 24.0; SPSS Inc., Chicago, IL, USA).

Results

A total of 195 eyes of 195 patients with glaucoma who met the inclusion and exclusion criteria were included in the study. Of the 195 eyes, 14 eyes (7.2%) were excluded from further analysis because the OCT-A images were of poor quality or the MvD was not clearly contoured. Interobserver agreement in terms of MvD was excellent (κ = 0.913; 95% confidence interval [CI] = 0.890–0.958).

Of 181 eyes, 58 (32.0%) had a single nonrecurrent DH and the remaining 63 (34.8%) had more than one DH during

Table 1. Characteristics of Open-Angle Glaucoma Patients With Non-Recurrent or Recurrent Disc Hemorrhage

	No DH (*n* = 60)	NonRecurrent DH (*n* = 58)	Recurrent DH (*n* = 63)	*P* Value[1]	*P* Value[2]
Age, y	55.83 ± 12.54	56.45 ± 13.37	59.79 ± 11.79	0.310*	0.146*
Gender, Male:Female	25:35	17:41	24:39	0.358†	0.204†
Diagnosis, *n* (%)				0.776†	0.465†
Primary open-angle glaucoma	10 (16.7%)	7 (12.1%)	9 (14.3%)		
Normal-tension glaucoma	50 (83.3%)	51 (87.9%)	54 (85.7%)		
Central corneal thickness, µm	532.86 ± 27.44	523.47 ± 37.57	530.04 ± 29.51	0.454*	0.510*
Spherical equivalent, diopters	−1.10 ± 2.54	−1.43 ± 2.71	−1.73 ± 3.05	0.620*	0.739*
Axial length, mm	24.52 ± 1.62	24.06 ± 1.32	24.40 ± 1.60	0.721*	0.512*
Baseline intraocular pressure, mm Hg	14.81 ± 2.77	14.86 ± 2.82	14.79 ± 2.76	0.820*	0.893*
Baseline average RNFL thickness, µm	78.62 ± 10.75	79.35 ± 11.16	79.21 ± 10.89	0.916*	0.943*
VF parameters					
Baseline MD of VF, dB	−3.65 ± 5.02	−3.64 ± 4.25	−3.69 ± 4.26	0.823*	0.951*
Baseline PSD of VF, dB	4.37 ± 3.65	4.25 ± 3.60	4.59 ± 3.76	0.650*	0.601*
MD slope, dB/y	−0.15 ± 0.53	−0.16 ± 0.47	−0.97 ± 2.20	**0.043***	**0.007***
PSD slope, dB/y	0.19 ± 0.44	0.20 ± 0.46	0.72 ± 0.78	**0.011***	**<0.001***
Central progression, *n* (%)	7 (11.7%)	9 (15.5%)	26 (41.3%)	**<0.001†**	**0.002†**
Location of DH, *n* (%)					**0.004†**
Inferotemporal		37 (63.8%)	48 (76.2%)		
Superotemporal		8 (13.8%)	14 (22.2%)		
Temporal		9 (15.5%)	1 (1.6%)		
Elsewhere		4 (6.9%)	0 (0%)		
Systemic factors, *n* (%)					
Diabetes mellitus	3 (5.0%)	6 (10.3%)	6 (9.5%)	0.521†	0.559†
Systemic hypertension	4 (6.7%)	6 (10.3%)	11 (17.7%)	0.163†	0.185†
Aspirin medication	3 (5.0%)	5 (8.6%)	12 (19.4%)	0.069†	0.076†
Vascular symptoms	1 (1.7%)	1 (1.7%)	15 (23.8%)	**<0.001†**	**<0.001†**
OCT-A findings					
Presence of MvD, *n* (%)	5 (10.0%)	16 (27.6%)	28 (44.4%)	**<0.001†**	**0.041†**
Follow-up periods, y	5.83 ± 1.11	5.71 ± 1.07	5.90 ± 1.20	0.560*	0.343*

DH, disc hemorrhage; MD, mean deviation; MvD, microvasculature dropout; OCT-A, optical coherence tomography-angiography; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; VF, visual field.

Data are mean ± standard deviation unless otherwise indicated.

Statistically significant differences between groups ($P < 0.05$) are indicated in bold.

* *P* value[1] from post hoc comparison and *P* value[2] from Student's *t*-test.

† Chi-square test.

Table 2. Characteristics of Open-Angle Glaucoma Patients With Non-Recurrent Disc Hemorrhage With or Without Baseline Microvasculature Dropout on Optical Coherence Tomography Angiography

	NonRecurrent DH With MvD (n = 16)	NonRecurrent DH Without MvD (n = 42)	P Value
Age, y	55.37 ± 14.90	56.85 ± 12.91	0.709*
Gender, Male:Female	4:12	13:29	0.460†
Diagnosis, n (%)			
Primary open-angle glaucoma	0 (0%)	7 (16.7%)	0.090†
Normal-tension glaucoma	16 (100%)	35 (83.3%)	
Central corneal thickness, µm	510.57 ± 20.61	529.92 ± 42.91	0.277*
Spherical equivalent, diopters	−0.54 ± 2.95	−1.82 ± 2.61	0.348*
Axial length, mm	23.34 ± 1.07	24.46 ± 1.32	0.134*
Baseline intraocular pressure, mm Hg	14.18 ± 2.76	15.11 ± 2.83	0.265*
Baseline average RNFL thickness, µm	84.50 ± 8.50	77.39 ± 11.51	**0.029***
VF parameters			
Baseline MD of VF, Db	−2.15 ± 2.57	−4.21 ± 4.64	0.690*
Baseline PSD of VF, dB	3.29 ± 2.68	4.61 ± 3.86	0.311*
MD slope, dB/y	−0.45 ± 0.51	−0.05 ± 0.40	**0.003***
PSD slope, dB/y	0.57 ± 0.56	0.05 ± 0.32	**<0.001***
Central progression, n (%)	7 (43.8%)	2 (4.8%)	**0.001**†
Location of DH, n (%)			0.281†
Inferotemporal	13 (81.2%)	24 (57.1%)	
Superotemporal	2 (12.5%)	6 (14.3%)	
Temporal	1 (6.2%)	8 (19.0%)	
Elsewhere	0 (0%)	4 (9.5%)	
Systemic factors, n (%)			
Diabetes mellitus	1 (6.2%)	5 (11.9%)	0.466†
Systemic hypertension	1 (6.2%)	5 (11.9%)	0.466†
Aspirin medication	0 (0%)	5 (11.9%)	0.186†
Vascular symptoms	1 (6.2%)	0 (0%)	0.276†
Follow-up periods, y	5.81 ± 1.32	5.66 ± 0.98	0.346*

DH, disc hemorrhage; MD, mean deviation; MvD, microvasculature dropout; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; VF, visual field.

* Student's t-test.

† Chi-square test.

Data are mean ± standard deviation unless otherwise indicated.

Statistically significant differences between two groups ($P < 0.05$) are indicated in bold.

the follow-up period. Sixty eyes (33.1%) with no history of DH were presented as a control group. The demographic features of the participants with no DH, nonrecurrent DH, and recurrent DH are presented in Table 1. The eyes with no DH, nonrecurrent DH, and recurrent DH had similar baseline characteristics, including age, baseline IOP, RNFL thickness, and MD of the VF. Mean follow-up periods were 5.83 ± 1.11 years in the no DH group, 5.71 ± 1.07 years in the non-recurrent DH group and 5.90 ± 1.20 years in the recurrent DH group ($P = 0.560$). VF progression expressed as MD slope was more prominent with the recurrent DH group (−0.97 ± 2.20 dB/year) than the nonrecurrent DH group (−0.16 ± 0.47 dB/year, $P = 0.007$) and central VF progression was significantly more frequent in the recurrent DH group (41.3%) than the nonrecurrent DH group (15.5%, $P = 0.002$). Systemic factors, such as diabetes mellitus, systemic hypertension, and aspirin medication were not different among the three groups ($P = 0.521$, $P = 0.163$, and $P = 0.069$, respectively); however, the presence of vascular symptoms was more frequent in the recurrent DH group (23.8%) than the nonrecurrent DH group (1.7%) and no DH group (1.7%, $P < 0.001$). Presence of MvD was more frequent in the recurrent DH group (44.4%) than the nonrecurrent DH group (27.6%, $P = 0.041$).

In the 58 eyes with nonrecurrent DH, the presence of MvD was further evaluated (Table 2). There were 16 eyes of nonrecurrent DH with MvD (27.6%) and 42 eyes of nonrecurrent DH without MvD (72.4%). Nonrecurrent DH with MvD group had more prominent VF progression (MD slope, −0.45 ± 0.51 dB/year) and more frequent central VF progression (43.8%) than nonrecurrent DH without MvD (MD slope = −0.05 ± 0.40 dB/year, $P = 0.003$ and central VF progression = 4.8%, $P = 0.001$), even when nonrecurrent DH eyes with MvD had thicker baseline RNFL thickness (84.50 ± 8.50 mm) than nonrecurrent DH eyes without MvD (77.39 ± 11.51 mm, $P = 0.029$).

Logistic regression analyses were performed to determine factors associated with central VF progression (Table 3). Presence of DH ($\beta = 2.72$, 95% CI = 1.01–5.41, $P < 0.001$), recurrent DH at different locations ($\beta = 3.24$, 95% CI = 2.41–5.13, $P < 0.001$), presence of vascular symptoms ($\beta = 5.54$, 95% CI = 2.01–8.32, $P < 0.001$) and MvD ($\beta = 4.52$, 95% CI = 2.34–7.77, $P < 0.001$) were the factors significantly associated with central VF progression in the multivariate analysis.

The recurrent DH group was further classified according to the presence of MvD at the DH location (Table 4). There were 28 eyes of recurrent DH with MvD (44.4%) and 35 eyes of recurrent DH without MvD (55.6%). Recurrent DH in MvD group experienced more frequent central VF progression (71.4%) than recurrent DH without MvD group (17.1%, $P < 0.001$). Recurrent DH without MvD group had greater frequency to present with DH recurrence at different locations (42.9%) and more vascular symptoms (37.1%) than

Table 3. Factors Associated With Central Visual Field Progression

	Univariate		Multivariate	
Variables	**Beta (95% CI)**	***P* Value**	**Beta (95% CI)**	***P* Value**
Age, y	0.98 (0.94–1.03)	0.420		
Female gender	1.53 (0.74–3.15)	0.556		
Diagnosis of NTG	1.05 (0.31–3.23)	0.831		
Central corneal thickness, µm	0.99 (0.97–1.03)	0.630		
Axial length, mm	0.56 (0.44–1.01)	0.232		
Mean baseline IOP, mm Hg	0.91 (0.76–1.08)	0.311		
Baseline average RNFL thickness, µm	1.04 (0.99–1.10)	0.136		
Baseline MD of VF (for each dB worse)	0.82 (0.70–0.99)	**0.008**	0.89 (0.64–1.34)	0.477
Baseline PSD of VF (for each dB worse)	1.13 (1.00–1.32)	**0.033**	1.21 (0.96–1.45)	0.105
Presence of DH	2.42 (1.11–3.54)	**<0.001**	2.72 (1.01–5.41)	**<0.001**
Recurrent DH	1.12 (1.00–1.32)	**0.047**	1.00 (0.98–1.03)	0.246
Recurrent DH at different locations	3.48 (1.83–7.52)	**0.007**	3.24 (2.41–5.13)	**<0.001**
Medication of diabetes mellitus	1.32 (0.73–2.04)	0.832		
Medication of systemic hypertension	1.01 (0.54–1.57)	0.410		
Aspirin medication	1.35 (0.92–2.01)	0.325		
Vascular symptoms	5.47 (1.33–9.13)	**0.030**	5.54 (2.01–8.32)	**<0.001**
Presence of MvD	4.13 (1.35–7.37)	**<0.001**	4.52 (2.34–7.77)	**<0.001**
Follow-up period	0.99 (0.41–1.39)	0.316		

DH, disc hemorrhage; IOP, intraocular pressure; MD, mean deviation; MvD, microvasculature dropout; NTG, normal tension glaucoma; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; VF, visual field.

Factors with statistical significance are shown in bold.

Table 4. Characteristics of Open-Angle Glaucoma Patients With Recurrent Disc Hemorrhage With or Without Baseline Microvasculature Dropout on Optical Coherence Tomography Angiography

	Recurrent DH With MvD (*n* = 28)	**Recurrent DH Without MvD (*n* = 35)**	***P* Value**
Age, y	59.78 ± 11.76	59.80 ± 11.98	0.996*
Gender, Male:Female	13:15	11:24	0.169†
Diagnosis, *n* (%)			
Primary open-angle glaucoma	5 (17.9%)	4 (11.4%)	0.356†
Normal-tension glaucoma	23 (82.1%)	31 (88.6%)	
Central corneal thickness, µm	526.42 ± 32.97	534.64 ± 25.20	0.502*
Spherical equivalent, diopters	−2.43 ± 3.54	−0.67 ± 1.79	0.163*
Axial length, mm	24.77 ± 1.87	23.85 ± 0.93	0.214*
Baseline intraocular pressure, mm Hg	14.25 ± 3.09	15.22 ± 2.42	0.165*
Baseline average RNFL thickness, µm	80.33 ± 12.13	78.31 ± 9.88	0.469*
VF parameters			
Baseline MD of VF, dB	−4.12 ± 5.55	−3.35 ± 4.19	0.533*
Baseline PSD of VF, dB	5.08 ± 4.13	4.21 ± 3.45	0.363*
MD slope, dB/y	−1.43 ± 3.16	−0.60 ± 0.75	0.139*
PSD slope, dB/y	0.94 ± 0.78	0.56 ± 0.74	0.055*
Central progression, *n* (%)	20 (71.4%)	6 (17.1%)	**<0.001**†
Location of DH, *n* (%)			0.529†
Inferotemporal	21 (75.0%)	27 (77.1%)	
Superotemporal	6 (21.4%)	8 (22.9%)	
Temporal	1 (3.6%)	0 (0%)	
Elsewhere	0 (0%)	0 (0%)	
Recurrence at different location, *n* (%)	4 (14.3%)	15 (42.9%)	**0.013**†
Systemic factors, *n* (%)			
Diabetes mellitus	2 (7.1%)	4 (11.4%)	0.449†
Systemic hypertension	6 (22.2%)	5 (14.3%)	0.315†
Aspirin medication	6 (22.2%)	6 (17.1%)	0.426†
Vascular symptoms	2 (7.1%)	13 (37.1%)	**0.005**†
Follow-up periods, y	5.92 ± 1.15	5.88 ± 1.25	0.346*

DH, disc hemorrhage; MD, mean deviation; MvD, microvasculature dropout; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; VF, visual field.

* Student's *t*-test.

† Chi-square test.

Data are mean ± standard deviation unless otherwise indicated.

Statistically significant differences between two groups ($P < 0.05$) are indicated in bold.

Table 5. Factors Associated With Recurrent Disc Hemorrhage

	Univariate		Multivariate	
Variables	**Beta (95% CI)**	***P* Value**	**Beta (95% CI)**	***P* Value**
Age, y	1.02 (0.99–1.05)	0.147		
Female gender	1.48 (0.69–3.18)	0.309		
Diagnosis of NTG	1.10 (0.38–3.17)	0.867		
Central corneal thickness, µm	0.99 (0.97–1.02)	0.629		
Axial length, mm	0.56 (0.28–1.12)	0.101		
Mean baseline IOP, mm Hg	0.99 (0.87–1.13)	0.892		
Baseline average RNFL thickness, µm	0.10 (0.97–1.03)	0.942		
Baseline MD of VF (for each dB worse)	0.10 (0.99–1.08)	0.951		
Baseline PSD of VF (for each dB worse)	1.03 (0.93–1.13)	0.598		
Medication of diabetes mellitus	1.10 (0.33–3.61)	0.880		
Medication of systemic hypertension	1.87 (0.64–5.43)	0.251		
Aspirin medication	2.54 (0.64–7.74)	0.100	2.17 (0.65–7.22)	0.206
Vascular symptoms	7.81 (2.27–13.98)	**0.006**	7.83 (2.71–12.59)	**0.004**
Presence of MvD	2.10 (0.98–4.49)	0.056	2.69 (1.19–6.04)	**0.018**
Follow-up period	0.82 (0.65–1.00)	0.972		

IOP, intraocular pressure; MD, mean deviation; MvD, microvasculature dropout; NTG, normal tension glaucoma; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; VF, visual field.

Factors with statistical significance are shown in bold.

Table 6. Factors Associated With Recurrent Disc Hemorrhage at Different Locations

	Univariate		Multivariate	
Variables	**Beta (95% CI)**	***P* Value**	**Beta (95% CI)**	***P* Value**
Age, y	0.99 (0.94–1.03)	0.543		
Female gender	1.02 (0.33–3.12)	0.971		
Diagnosis of NTG	0.64 (0.12–3.66)	0.641		
Central corneal thickness, µm	1.00 (0.98–1.02)	0.970		
Axial length, mm	1.21 (0.63–2.32)	0.566		
Mean baseline IOP, mm Hg	0.97 (0.81–1.18)	0.782		
Baseline average RNFL thickness, µm	1.02 (0.97–1.07)	0.445		
Baseline MD of VF (for each dB worse)	0.98 (0.83–0.15)	0.790		
Baseline PSD of VF (for each dB worse)	1.07 (0.92–1.25)	0.361		
Medication of diabetes mellitus	1.61 (0.25–5.50)	0.620		
Medication of systemic hypertension	1.65 (0.31–8.82)	0.556		
Aspirin medication	1.64 (0.41–6.67)	0.486		
Vascular symptoms	5.27 (2.83–8.24)	**0.002**	6.08 (2.17–10.37)	**0.004**
Presence of MvD	0.23 (0.06–0.88)	**0.033**	0.32 (0.07–1.38)	0.126
Follow-up period	1.01 (0.99–1.03)	0.552		

IOP, intraocular pressure; MD, mean deviation; MvD, microvasculature dropout; NTG, normal tension glaucoma; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; VF, visual field.

Factors with statistical significance are shown in bold.

recurrent DH with MvD group (14.3%, $P = 0.013$ and 7.1%, $P = 0.005$, respectively).

Logistic regression analyses were performed to determine factors associated with recurrent DH (Table 5). Presence of vascular symptoms ($\beta = 7.81$, 95% CI = 2.27–13.98, $P = 0.006$) was the significant factor associated with the recurrent DH in the univariate analysis and also in the multivariate analysis ($\beta = 7.83$, 95% CI = 2.71–12.59, $P = 0.004$) along with the presence of MvD at the DH location ($\beta = 2.69$, 95% CI = 1.19–6.04, $P = 0.018$). In the regression analysis, to determine the factors associated with DH recurrence at different locations (Table 6), the presence of vascular symptoms ($\beta = 5.27$, 95% CI = 2.83–8.24, $P = 0.002$) and not accompanying MvD ($\beta = 0.23$, 95% CI = 0.06–0.88, $P = 0.033$) were significant factors in the univariate analysis. Among these factors, the presence of vascular symptoms ($\beta = 6.08$, 95% CI = 2.17–10.37, $P = 0.004$) was the factor significantly associated with the DH recurrence at different locations in the multivariate analysis. In the Kaplan-Meier analysis, the groups with recurrent DH demonstrated a higher cumulative probability of central VF progression compared to the single DH groups, irrespective of the presence of MvD. Within both the single and recurrent DH groups, eyes with MvD exhibited a higher cumulative probability of central VF progression (log rank test, $P < 0.001$; Fig. 1).

A representative example is shown in Figure 2. A 51-year-old woman diagnosed with NTG in her left eye exhibited MvD at the inferotemporal location. She experienced an initial DH at the same inferotemporal location, followed by a recurrence at the same site. The DH recurred twice during the follow-up period. There was significant enlargement of localized RNFL defects and VF progression after 45 months (MD slope = −0.81 dB/year). A contrasting representative case is shown in Figure 3, in which a 76-year-old man diagnosed with NTG in his left eye, without MvD,

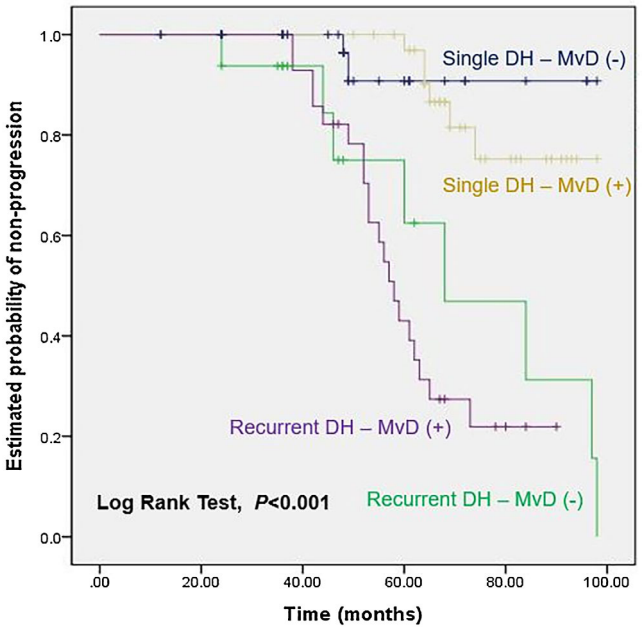

Figure 1. Kaplan-Meier analysis of the probability to remain without central visual field progression in glaucoma patients. The groups were divided based on the occurrence of either a single or recurrent disc hemorrhage, as well as the presence of microvasculature dropout. The application of the log rank test revealed a statistically significant difference between these groups.

had an initial DH at the superotemporal location. Subsequently, there was a recurrence at different locations in the inferotemporal region. The DH recurred four times during the follow-up period, and he temporarily experienced DH recurrence at both the superotemporal and inferotemporal locations. The localized RNFL defect became more prominent, and VF progression was noted throughout 96 months (MD slope = −0.59 dB/year).

Discussion

We focused on the DH recurrence and the clinical significance of the accompanying MvD at the DH site. Eyes with DH accompanied by MvD show more pronounced central VF progression. In the presence of MvD, recurrent DH is more likely to occur at the same location, whereas recurrent DH without MvD exhibits more frequent vascular symptoms and tends to recur at different sites. This suggests that MvD acts as a mechanical factor, deforming the lamina cribrosa and peripapillary sclera, with vessels under compression becoming recurrence sites, leading to progression at the same location. The presence of MvD at the DH site serves as a biomarker predicting future progression, especially in central VF. DH with MvD has a higher likelihood of recurring at the same site via a mechanical mechanism, making further IOP lowering beneficial in preventing progression in these patients with glaucoma. Conversely, vascular factors may contribute to DH recurrence in the absence of MvD, leading to recurrent DH at various sites due to potential blood flow instability affecting the entire ONH region. Patients with recurrent DH without MvD and recurrence at different sites on the disc may require evaluation of vascular factors. Mechanical compression of the vessels at the ONH, observed as MvD with recurring DH at that site, and vascular symptoms related to blood flow instability to the ONH with recurring DH at different sites, both contribute to VF progression. Therefore, we could assume the underlying mechanism and customize glaucoma patients with DH using OCT-A.

MvD was a finding that was more frequently detected in OAG eyes with DH compared with eyes without DH in our previous study,[21] and, in this study, MvD was more frequently detected with recurrent DH than nonrecurrent DH. MvD is a new ocular parameter that emerged with the introduction of the OCT-A device and is associated with progressive RNFL thinning and VF progression.[12,21,31] The pathogenesis of MvD has not been clearly elucidated; however, mechanical processes are known to be crucial for its development. MvD was found to be more preva-

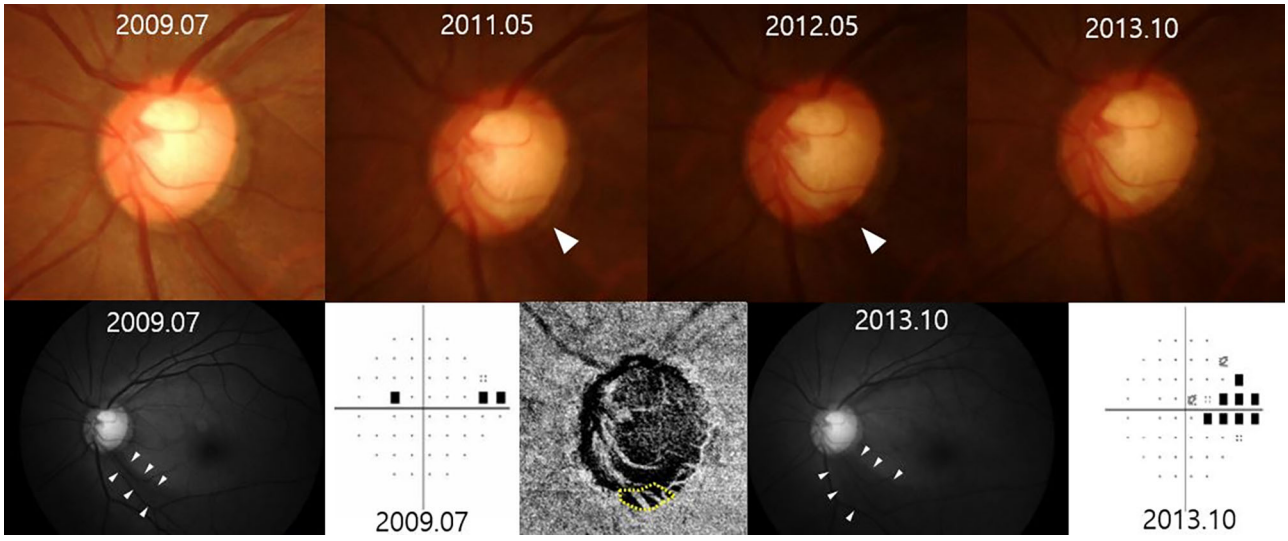

Figure 2. A representative case of normal tension glaucoma eye with disc hemorrhage (DH) recurring at the inferotemporal location with microvasculature dropout (MvD) (*yellow dotted line*). Recurrent DH occurred at the temporal border of a localized retinal nerve fiber layer defect. There was significant enlargement of localized RNFL defect and visual field progression after 45 months (mean deviation slope = −0.81 dB/year).

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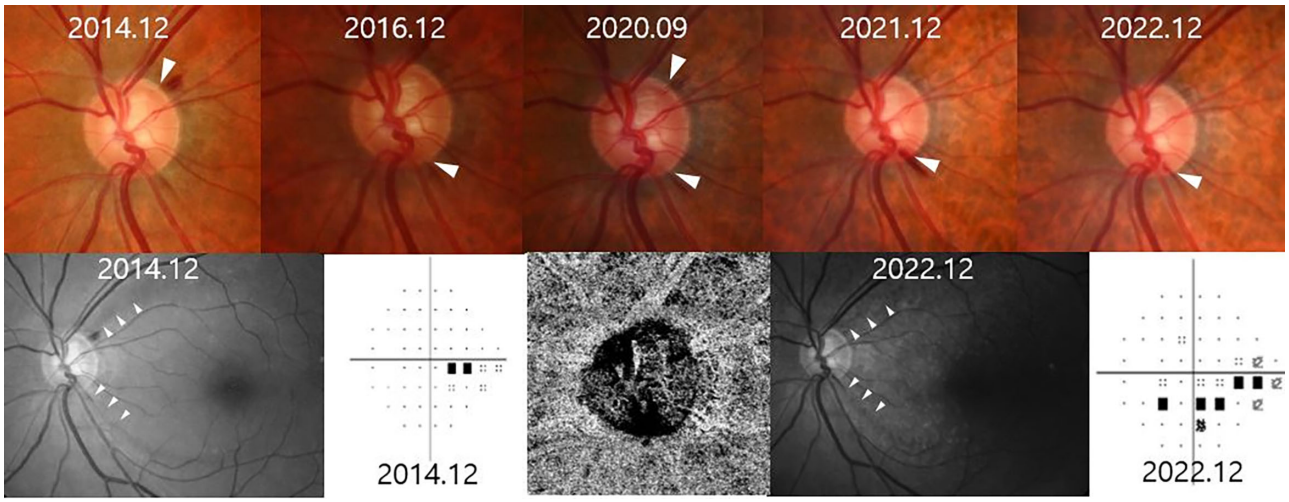

Figure 3. A representative case of normal tension glaucoma eye with disc hemorrhage (DH) recurring at superotemporal and inferotemporal locations, without microvasculature dropout (MvD). The localized superotemporal and inferotemporal retinal nerve fiber layer defects became more prominent throughout the follow-up period, and visual field progression was noted during 96 months (mean deviation slope = −0.59 dB/year).

lent in eyes with OAG than in eyes with branch retinal vein occlusion (BRVO) that exhibited similar VF defects.[32] Unlike BRVO, which leads to RNFL and superficial vessel density loss along with VF damage, the occurrence of MvD in OAG eyes appears to be associated with distinct mechanical insults within the ONH as part of the glaucomatous process. This distinction is not explained solely by vascular insufficiency observed in BRVO.

DH is a transient occurrence within the ONH and typically resolves within 6 to 12 weeks,[33] with no residual evidence of hemorrhage upon complete absorption. Conversely, MvD is thought to persist in the same location over the years once it becomes evident. We focused on the distinctive characteristics of two findings: DH, which can occur, vanish, and re-appear at the same or different locations, in contrast to MvD, a relatively permanent finding. Kim et al.[34] found that RNFL thinning was progressive at the location of MvD, accompanied by subsequent DH, and continued to progress after the occurrence of DH. Our study focused on the recurrence of DH and evaluated its progression in patients with concomitant MvD. To our knowledge, this is the first study to evaluate the presence of MvD in eyes with nonrecurrent and recurrent DH.

In our previous study, where we investigated DH using disc fluorescein angiography,[35] eyes with DH related to RNFL defects had blood-flow stasis at the site where the DH occurred. The structural changes in the ONH or RNFL were considered to be the cause of the hemodynamic changes at the DH location. As in our study, MvD might be considered as another cause contributing to the blood-flow stasis of the ONH or a result implying blood flow stasis, as the recurrent DH eyes with MvD had DH recurrence at the same location related to MvD. The MvD accompanied by BRVO and compressive optic neuropathy demonstrates that MvD occurs as a secondary change in RGC loss and focal dropout of the vessels as metabolic demand is reduced.[32,36] In our study, the presence of MvD showed a negative correlation with the recurrence of DH at different locations. This leads us to cautiously hypothesize that MvD is not merely an epiphenomenon or a secondary consequence of RGC loss but rather a dynamic factor actively influencing the hemodynamics of the ONH.

In our previous study,[28] we observed that eyes with recurrent DH at different locations from the initial DH sites exhibited more pronounced VF progression. However, in the present study, we found that recurrent DH with MvD was associated with greater central VF progression compared to recurrent DH without MvD, even when the latter group had more instances of DH recurrence at different locations. Our findings suggest that when vascular dysregulation, represented by DH, coincides with a mechanical factor, represented by MvD, there is a tendency for DHs to recur at the same site related to the MvD, leading to more prominent central VF progression. As MvD emerges as a critical mechanical factor contributing to central VF progression, it becomes imperative to exercise careful monitoring of eyes with vascular dysregulation, particularly when accompanied by MvD.

In our previous study,[28] DH recurring at different locations from the initial DH was associated with a history of more frequent aspirin use. Patients with recurrent DH were more likely to be taking aspirin than patients with nonrecurrent DH, although this difference did not reach statistical significance in the present study. The earlier study[28] attempted to elucidate the mechanical and vascular aspects of DH by categorizing recurrent DH based on location: DH recurring at the same location with more mechanical aspects, and DH recurring at different locations with more vascular aspects. In this study, we attempted to identify the mechanisms underlying DH by evaluating the presence of MvD using OCT-A. The finding that DH recurred more at different locations in the without-MvD group and recurred more at the same location in the MvD group reflects the mechanical aspect of MvD. Therefore, the presence of MvD not only suggests vascular insufficiency within the ONH, but also signifies concurrent mechanical changes within the ONH. This indicates compression of vessels within the deep ONH structures, resulting in both mechanical and vascular damage to the optic nerve. This may explain the greater progression of DH in eyes with MvD than in those

without MvD. Eyes with vascular symptoms had recurrent DH at different locations, indicating that these eyes may lack localized mechanical stress and compressed vessels. Nevertheless, vascular damage may contribute to progression due to the overall vascular insufficiency throughout the ONH.

Our study had some limitations. First, patients were followed-up at 1 to 3 month intervals, and because DHs usually last for 6 to 12 weeks,[33] there might have been DHs that occurred between the follow-up periods and were not detected. Participants with recurrent DH may have been misclassified as having nonrecurrent DH if only one DH episode was detected during the follow-up period. Additionally, a participant in the nonrecurrent DH group might have experienced additional DH cases in the future, highlighting a limitation inherent in the retrospective nature of this study. We attempted to alleviate this problem by including patients who had been followed up for at least 4 years because there is a report showing that cumulative probability of DH detection reaches plateau around 4 to 5 years of follow-up.[37] Second, the VF examination was only carried out as SITA 24-2. Because 10-2 VF examination had not been carried out, some of the cases who had milder central VF progression could have been overlooked, that our study only included central progression prominent on the 24-2 strategy only. Third, there may be a concern that the presence of DH might interfere with the detection of MvD, potentially leading to false dropouts and the underestimation of MvDs. We attempted to overcome this limitation by only including clear images with quality scores > 30, blinding the clinical data and independently identifying the MvDs by 2 independent observers. The presence of DH within the prelaminar area and surrounding superficial RNFL layer is thought to have minor impact on the vessel density measurements of choroidal layer.[38] In addition, all the MvDs were looked over when the DH resolved, and only eyes with MvD remaining at the site of previous DH was considered to have MvD. The vascular symptoms addressed in this study were history of migraine, Raynaud's phenomenon, cold extremities, or orthostatic hypotension. Further research is needed to assess vascular factors using more objective parameters, such as heart rate variability.[29]

In conclusion, we found that both DH occurrence and the presence of MvDs constitute critical parameters associated with central VF progression. In the presence of MvD, recurrent DH was more likely to recur at the same location as the MvD, whereas recurrent DH without MvD was related to vascular symptoms and recurred at other locations. Our analysis suggests an intricate connection between the two, with the presence of MvD exerting influence on the locations of DHs. This emphasizes the interplay among recurrent DHs, MvDs, and their collective impact on the central VF. When eyes present with recurrent DH and MvD, closer follow-up and more aggressive treatment are required to prevent the progression of central VF.

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