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Characteristics of Central Visual Field Progression in Eyes with Optic Disc Hemorrhage

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Abstract

Purpose: To investigate the characteristics and rate of central visual field loss after optic disc hemorrhages (DH).

Design: Prospective cohort study.

Methods: 343 eyes of 220 subjects who had at least 3 years of follow-up with minimum of 5 visits with 10-2 and 24-2 visual field (VF) were recruited. Rates of 10-2 mean deviation (MD) loss in each hemifield and pre-defined zones were compared using linear mixed-effects model in DH and non-DH eyes. Clustered pointwise regression analysis was also used to define central VF progressors and compared to 24-2 VF loss using Guided Progression Analysis.

Results: 39 eyes with DH and 304 eyes without DH had a mean follow-up of 5.2 years. Eyes with DH had rates of 10-2 mean deviation (MD) loss that were 3 times faster than non-DH eyes

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(mean difference (95% CI): −0.36 dB/year(0.54, 0.18), $p<0.001$) and were 3.7 times more likely to progress ($p=0.002$). A larger proportion of glaucomatous eyes showed central VF progression rather than peripheral VF progression in DH group (30.8% vs. 20.5%) compared to non-DH group (10.9% vs. 9.2%). In early glaucoma, the rate of 10-2 MD loss was 5.5 times faster in DH eyes than in non-DH eyes($p<0.001$). Superonasal and superotemporal central VF regions progressed more rapidly than other regions, especially in DH eyes.

Conclusion: Central visual field loss is accelerated in glaucoma eyes with DH and it corresponds topographically to the DH location. In glaucoma patients with DH, one should consider supplementing 10-2 VFs with 24-2 VFS to monitor the disease.

Keywords

central visual field; optic disc hemorrhage; glaucoma; progression

Introduction

Glaucoma is a progressive optic neuropathy characterized by the loss of retinal ganglion cells (RGCs) associated with degeneration of the optic nerve and retinal nerve fiber layer (RNFL).[1] Optic disc hemorrhages (DHs) are strongly associated with the development[2-4] and progression of glaucomatous damage.[5-10] Although the pathophysiology of glaucomatous DHs is unknown, several hypotheses have been proposed, including vascular and mechanical theories. It is known, however, that peripapillary DHs are topographically associated with localized RNFL defects and neuroretinal rim notching. Most notably, DHs occur at the border between healthy and damaged RNFL.[11]

The central visual field (VF) generally was thought to be preserved until advanced stages of disease.[12] However, recent studies reported that paracentral VF defects often are observed in early glaucoma.[13, 14] Early detection of macular involvement and its progression is of great importance because the loss of central vision can significantly affect an individual's quality of life. Central vision loss is associated with faster glaucoma progression and increased disability in performing daily tasks such as reading, driving and walking.[15-19]

It has been suggested that 24-2 testing strategies may be suboptimal VF test patterns to detect early macular involvement in glaucoma.[20-26] To evaluate central vision, clinicians often employ a 10-2 VF test which uses 68 central test points that are 2 degrees apart. However, such a strategy has been questioned. In a study by West et al[26], there was little benefit to also using 10-2 VF in revealing additional central VF defects in patients with early 24-2 VF defects. The authors suggested that use of 10-2 VF might be best employed for following patients with a high risk of central visual field progression.[26]

In recent studies, eyes with early glaucomatous defects in central areas were strongly associated with a history of DHs.[27-31] However, information about the spatial relationship and rate of central VF progression in disc hemorrhages is sparse. In the current study, the characteristics, rates, and relationships of central VF loss with the location of DHs were investigated and compared to eyes without DH. We also tested whether DH eyes experience

more rapid peripheral and central visual field loss than non-DH eyes as measured with the entire 24-2 VF and 10-2 VF test patterns.

Methods

Participants

In this observational cohort study, participants were included from a prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma (Diagnostic Innovations in Glaucoma Study [DIGS] and African Descent and Glaucoma Evaluation Study [ADAGES]). Participants in these cohorts were longitudinally evaluated according to a pre-established protocol that included regular follow-up visits in which patients underwent a clinical examination and several imaging and functional tests. All participants from the DIGS and ADAGES study who met the inclusion criteria described below were enrolled in the current study. Informed consent was obtained from all participants. The University of California, San Diego Human Subjects Committee approved all protocols, and the methods described adhered to the tenets of the Declaration of Helsinki.

Subjects underwent annual comprehensive ophthalmologic examination, including review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, dilated funduscopic examination, stereoscopic optic disc photography, and standard automated perimetry using a Full-Threshold or Swedish Interactive Threshold Standard Algorithm (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA). Semi-annual examinations included standard automated perimetry (10-2 VF and 24-2 VF) and IOP measurement. Only subjects with open angles on gonioscopy at baseline were included. Subjects were excluded if they had a baseline best-corrected visual acuity less than 20/40, spherical refraction with greater than 6.0 diopters of myopia, cylinder correction greater than 3.0 diopters, or any ocular or systemic disease that could affect the optic nerve or visual field.

The study included eyes diagnosed as glaucoma or glaucoma suspect with or without history of DH at the baseline visit with a minimum follow-up time of 3 years and a minimum of five 10-2 and 24-2 VFs. Eyes were classified as glaucomatous if they had repeatable (at least 2 consecutive) abnormal VF test results or evidence of glaucomatous optic neuropathy defined as excavation, the presence of focal thinning, notching of neuroretinal rim, or localized or diffuse atrophy of the RNFL on the basis of masked grading of optic disc photographs by 2 graders or clinical examination by a glaucoma specialist. An abnormal VF test was defined as a pattern standard deviation outside of the 95% normal confidence limits or a Glaucoma Hemifield Test result outside normal limits. Glaucoma suspects were defined as having elevated IOP (≥22mmHg) or suspicious-appearing optic discs without the presence of repeatable glaucomatous VF damage.

Stereophotography

All patients had stereoscopic optic disc photographs repeated at least every 12 months during follow-up. The presence of an optic disc hemorrhage was evaluated by two experienced graders using a stereoscopic viewer (Screen-VU stereoscope; PS

Manufacturing, Portland, OR). Each grader was masked to the subject's identity and the other test results. All included photographs were judged to be of adequate quality or better. Discrepancies between the two graders were resolved by consensus or adjudication by a third experienced grader. DHs had to be located within one-half disc diameter of the optic disc border and not associated with optic disc edema, papillitis, diabetic retinopathy, central or branch retinal vein occlusion, or any other retinal disease.[32, 33] The locations of DHs were categorized as located in the superior hemisphere, inferior hemisphere, or both.

Standard Automated Perimetry

The 10-2 and 24-2 VF tests were considered unreliable and excluded if there was >33% fixation losses, >33% false-positive errors, or >33% false-negative errors. Experienced graders at the University of California, San Diego Visual Field Assessment Center (VisFACT) reviewed all the results, excluding tests with eyelid or rim artifacts, fatigue or learning effects, inappropriate fixation, or evidence that the visual field results were caused by a disease other than glaucoma (e.g. homonymous hemianopia) or inattention. Patients with glaucoma were stratified into 2 categories based on the severity of their VF damage. Patients with mean deviation (MD) >−6.0 dB were classified as mild glaucoma, and patients with MD≤−6.0 were classified as moderate to severe glaucoma.[34]

The regions corresponding to the structure versus function map for 10-2 VFs proposed by Hood et al[13] (Figure 1) were divided into five zones: the superior nasal (Zone 1), superior temporal (Zone 2), superior temporal band (Zone 3), inferior temporal (Zone 4), and inferior nasal (Zone 5). For calculation of the mean deviation (MD) in each zones, threshold sensitivity values in decibels (dB) were used. The MDs of the zones were calculated as the average threshold sensitivity values of all points tested in that region.

Central Visual Field Progression

Different trend-based analyses were used to characterize progression in the 10-2 VF tests are described below.

Best Linear Unbiased Prediction: Estimates of rates of change for individual eyes and different zones were obtained by best linear unbiased prediction (BLUP). Ordinary least square estimates can be imprecise in eyes with just a few measurements available over time or with large intraindividual variability.[35] Individual ordinary least square estimates (i.e., individual regression lines) also do not take into account the information provided by the whole population, whereas BLUPs are shrinkage estimates that take into account the results obtained by evaluating the whole sample of eyes, giving less weight to estimates obtained from eyes with few measurement occasions or large intraindividual variability (i.e., more "noise").[36] In eyes with a large number of measurements over time, BLUP and ordinary least square estimates give similar results. BLUPs have been used to estimate individual rates of structural change measured by different instruments in glaucoma, and rate of cognitive change in longitudinal models.[37, 38]

Clustered Pointwise Linear Regression: Regression of VF parameters over time has been used to identify VF deterioration and to estimate magnitude of VF loss. Regression of

individual locations or of clusters provided more information about the location of VF loss than could regression of global indices.[39, 40] A VF test point was flagged as worsening if it showed a significant negative slope of at least −1 dB/year, with a significance level of $p<0.01$.[41, 42] As in de Moraes et al., progression in a 10-2 VF was defined as at least 3 test points located in the same latent class analysis (LCA) derived 10-2 VF sector progressing faster than −1.0 dB/year at $p<0.01$.[43]

Peripheral Visual Field (24-2) Progression

24-2 VF progression was defined when there were >3 locations that showed a significant change (ie, change greater than the test-retest variabilities) compared with 2 baseline examinations for at least 3 consecutive tests (ie, “likely progression” as reported in the Guided Progression Analysis [GPA]) during the study follow-up and when the changes also were observed at the latest follow-up visit.[44]

Statistical analysis

Continuous and categorical data were presented as mean (95% confidence interval, CI) and count (%). Statistically significant differences in patient characteristics between the DH group and the non-DH group were determined by two-sample t-tests for continuous variables and Fisher’s exact test for categorical variables. Eye characteristics were compared using linear mixed effects models with random intercepts to account for within-subject variability. VF trajectories were estimated using linear mixed effects models with random eye-within-patient intercepts and independent random slopes-within-eye. These models include fixed effect for DH history and time interaction. Multivariable models were fit including age, mean IOP over follow-up, as well as any other ocular characteristic reported to be associated with progression in previous studies and whose p value was below 0.10 in univariable analysis.

Logistic regression was used to compare progressors versus non-progressors assessed by clustered PLR analysis or GPA analysis. Multivariable logistic regression was performed to explore factors contributing to progressive 10-2 mean deviation (MD) loss.

Linear mixed-effect models with random intercepts and random slopes were also used to compare the rate of 10-2 MD loss in each hemifield and each zone between DH and non-DH eyes. Similarly, rates of MD loss in the hemifield corresponding to DHs of DH eyes were calculated and compared to the rates of central MD loss in non-corresponding hemifields of DH eyes and non-DH eyes. All statistical analyses were conducted using Stata/IC version 13.0 (StataCorp, Texas, USA).

Results

Three hundred forty three eyes from 220 patients met our inclusion criteria and were included in this report. Mean age (95% CI) at baseline was 71.1 (67.8, 74.5) years for the disc hemorrhage (DH) group and 68.1 (66.7, 69.5) years for the non-DH group ($p=0.089$). The number of visits were comparable between 24-2 VF ($p=0.212$) and 10-2 VF ($p=0.497$) visits. Eyes with DH had a mean number (95% CI) of 7.8 (7.2, 8.5) 10-2 VFs and 7.9 (7.2, 8.7) 24-2 VFs over 5.1 (4.9, 5.2) years, while non-DH eyes had 7.6 (7.3, 7.8) 10-2 VFs

and 7.7 (7.4, 8.0) 24-2 VFs over 5.3 (5.2, 5.5) years. Baseline 24-2 MD and 10-2 MD were similar in both groups (p=0.867 and p=0.825, respectively). Of the 39 eyes with DH, the DH was located inferiorly in 28 (71.8%) eyes, superiorly in 4 (10.3%) eyes, and in both hemispheres in 7 (17.9%) eyes. Patient characteristics are summarized in Table 1.

Central visual field (VF) mean deviation (MD) deteriorated in both DH eyes and non-DH eyes. Eyes with DH had rates of 10-2 MD loss three times faster than non-DH eyes (mean difference (95% CI): −0.36 dB/year (0.54, 0.18), p<0.001).

Differences in rates of 10-2 MD loss were also found between DH and non-DH groups when comparing the hemifields. Eyes with DH had a faster rate of 10-2 MD loss in both superior hemifields (−0.31 dB/year (−0.50, −0.12), p=0.001) and inferior hemifields (−0.18 dB/year (−0.36, 0.01, p=0.037) compared to non-DH eyes (Table 2). Among DH eyes, faster rates of MD loss were found in the superior hemifield (mean (95% CI): −0.48 dB/year (−0.65, −0.30) compared to the inferior hemifield (−0.32 dB/year (−0.49, −0.16). Similar results were found after adjusting for age and baseline 24-2 MD. A history of DH (p<0.001) and lower baseline 24-2 MD (p<0.001) were associated with faster 10-2 MD loss in the multivariable analysis (Table 3).

Using the clustered PLR criteria, central VF progression was seen in 12 of the 39 (30.8%) eyes in the DH group and 33 of the 304 (10.9%) eyes in the non-DH group. Although a similar proportion of 24-2 progression was found in the non-DH group (28 eyes, 9.2%), a lower proportion of DH eyes were progressors in 24-2 VF (8 eyes, 20.5%) compared to 10-2 VF.Table 4 shows the univariable and multivariable logistic regression analyses results of factors associated with 10-2 VF progression defined by clustered pointwise linear regression (PLR) of MD. In univariable analysis, history of DH (Odds Ratio (OR): (95% CI): 3.65 (1.58, 8.42); p=0.002), worse baseline 10-2 VF MD (OR: 1.04 (0.99, 1.09) per 1 dB; p=0.096) and worse baseline 24-2 VF MD (OR: 1.06 (1.02, 1.11) per 1 dB; p=0.004) were associated with 10-2 VF progression. As both baseline 10-2 MD and 24-2 MD were significantly correlated with each other, these two VF parameters were included in separate multivariable models to avoid multicollinearity. In both multivariable models, DH was significantly associated with VF progression (OR: 3.78 (1.56, 9.13), p=0.003; OR: 3.51 (1.48, 8.29), p=0.004, in models adjusting for 24-2 and 10-2 VF MD, respectively).

When evaluating different VF zones between DH and non-DH eyes, superior nasal (Zone 1), superior temporal (Zone 2), superior temporal band (Zone 3), and inferior nasal (Zone 5) zones had significantly faster rates of MD loss compared to the inferior temporal (Zone 4) zone (Table 5). The distributions of the mean rates of 10-2 VF loss for DH and non-DH eyes are presented in Figure 2. Similar results were found when comparing the zones in 28 eyes with inferior DH and those of non-DH eyes (Supplemental Table 1).

The topographic location of DH was associated with higher rates of central VF loss. Of the 28 eyes in which the DH was located in the inferior hemisphere, the mean difference between the rates of 10-2 MD loss in the corresponding hemifield (mean (95% CI): −0.24 dB/year (−0.45, −0.03), p=0.026) was faster than the non-corresponding hemifield (−0.10 dB/year (−0.29, −0.10), p=0.110).

The results were more pronounced in eyes with early glaucoma (24-2 VF MD >−6 dB). Rates of 10-2 MD loss in DH eyes with early glaucoma were 5.5 times faster than non-DH eyes (mean (95% CI) −0.56 dB/year (−0.71, −0.40), vs. −0.10 dB/year (−0.16, −0.04), $p<0.001$). After adjusting for confounders, eyes in the DH group were 4.4 times more likely to develop 10-2 VF progression ($p=0.003$) (Supplemental Table 2 and 3; Figure 3).

Although the DH eyes had faster rate of 24-2 MD deterioration compared to non-DH eyes, the difference did not reach statistical significance after adjusting for confounders in all eyes (mean difference (95% CI): −0.17 (−0.34, 0.01) dB/year, $p=0.112$) and was marginally significant in early glaucoma in early glaucoma (−0.15 (−0.26, −0.03) dB/year, $p=0.073$).

Discussion

The current study showed that rates of progressive central visual field (VF) loss in disc hemorrhage (DH) eyes were approximately three-fold faster than non-DH eyes, supporting the role of DH as an important risk factor for glaucoma progression. A larger proportion of eyes showed central, rather than peripheral, VF progression in the DH group compared to the non-DH group. Furthermore, early glaucoma patients with DH had an approximately five-fold faster rate of central mean deviation (MD) loss compared to non-DH eyes. This difference in the rate of progression was more evident in the superior hemifield with topographically associated inferiorly located DH. This information should help clinicians better understand the role of 10-2 VF as a supplement test to 24-2 VF in eyes with DH and provides clinical clues in monitoring glaucoma progression in these high-risk patients.

Associations between DH and perimetric progression,[45] optic disc changes,[5] retinal ganglion cell loss,[46] retinal nerve fiber layer thinning,[47] and vessel density dropout[48] have been demonstrated in various studies. In the Ocular Hypertension Treatment Study, there was a two-fold increase in the cumulative incidence of developing primary open angle glaucoma in eyes with DH.[49] De Moraes et al. studied VF progression before and after detection of DH and found that the 24-2 VF sector with the fastest progression predicted the location of future DHs in 85% of cases. The same VF sector maintained the fastest progression rate in almost all the eyes after the detection of DH.[7] Although several studies have shown that the rate of RNFL thinning and VF loss increases after DH,[45, 47] less was known about the rate and characteristics of central VF loss in eyes with DH. By evaluating the 10-2 VF in the current study, we demonstrated that the mean rate of central VF loss in DH eyes was −0.50 dB/year, almost three-fold faster than in non-DH eyes. Recent investigations found that DHs were associated with more central damage in 10-2 VFs.[27, 50] Kono et al. characterized VF progression in eyes with DH using 24-2 VFs and found that eyes with DH were associated with greater VF progression in areas within the central 10 degrees, whereas no significant differences were found in other clusters or in the whole field.[27] With analysis of progression using the clustered PLR criteria, we also confirmed prior studies and showed that the DH group had a three-fold increase in the number of eyes with central VF progression compared to non-DH eyes over 5 years of follow-up.

Hood et al. suggested that the inferior macular region was more susceptible to early glaucomatous damage than the superior macular region and coined the term “macular

vulnerability zone" to describe the 50% of inferotemporal arcuate RNFL fibers prone to glaucomatous damage.[13, 51] Traynis et al. showed that superior VF defects are deeper and closer to the fixation than those in the inferior VF.[15] Likewise, in the present study, the rate of central VF loss was faster in the superior hemifield compared to inferior hemifield. The association of DH location with both structural and functional loss in glaucoma have been described in previous studies.[52, 53] In the present study, DHs were predominantly detected in the inferotemporal region and rates of central VF deterioration were faster in the corresponding hemifield. The association between DH location and higher rates of central VF loss was further highlighted in our sub-analysis involving inferiorly located DHs; the rate of VF loss in the corresponding superior hemifield of these eyes was statistically significant higher compared to the non-corresponding inferior hemifield.

Macular involvement in early glaucoma is strongly correlated with a decline in vision-related quality of life (VRQoL) while arcuate damage outside the macula was less significant.[54] A recent study on patient's VRQoL found that it was also dependent on its hemifield location. Near activities were likely to be affected with superior field defect while distance activities with inferior field defect.[55] In our sub-analysis of central VF in eyes with early glaucoma, DH eyes had significantly faster rates of progression in both superior and inferior hemifields than non-DH eyes. Additionally, in DH eyes with early glaucoma, the superior temporal zone (Zone 2), which corresponds to the MVZ, had rates of progression which were three-fold faster than the rate of non-DH eyes. Given the substantial impact of central VF on quality of life, meticulous assessment of the central VF and its inherent affected functions is recommended in managing glaucoma patients with DH. In addition, early testing of 10-2 VF has been reported to be useful in detecting patients with initial parafoveal scotoma (IPFS) in glaucoma. In a study by Park et al, in patients with IPFS, the 10-2 VF performed better in detection of progressing eyes compared with 24-2 VF.[20]

This study has limitations. Though the study was sufficiently powered to detect changes in the central VF in DH eyes, there were few eyes with superiorly located DHs; thus, detailed characterization of central VF progression in these eyes was not possible. Next, the frequency of optic disc photos is a possible limitation as they were acquired annually even though DHs typically resolve within 2 to 6 months.[56] Therefore, it is possible that some DHs may have been missed in each group. Moreover, around 3.5 years on average elapsed between DH occurrence and baseline VF, therefore the rates of central VF loss should not be generalized to the time frame immediately following DH. In addition, the commercially analysis software built into the perimeters does not include analysis of progression of 10-2 fields which may make the use of 10-2 less relevant to most clinicians. Recently, development of a new algorithm for detecting progressive changes in 10-2 VF tests using event-based analysis has been described and validated[57] and, perhaps, it will be incorporated in available perimeters in the future. Last, this was not a prospective observational study. Clinical observations of DHs and 10-2 visual field defects may have led to intensification of IOP-lowering therapy, potentially decreasing the true effect of DH on the rates of central visual field loss.

In conclusion, disc hemorrhages are an independent predictor for more accelerated central VF loss in glaucoma, especially in early stages of the disease. Central VF loss was faster in

eyes with history of DH and worse visual fields at baseline. Moreover, superior hemifield defects tended to progress more rapidly than inferior hemifield defects in DH eyes. A larger proportion of eyes showed central VF progression rather than peripheral VF progression in the DH group compared the non-DH group. Therefore, examination of the central visual field using a 10-2 strategy should be considered in glaucoma patients with a history of DH for sensitive detection of disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

ADAGES	African Descent and Glaucoma Evaluation Study
BLUP	best linear unbiased prediction
CCT	central corneal thickness
CI	confidence interval
dB	decibel
DH	disc haemorrhage
DIGS	Diagnostic Innovations in Glaucoma Study
F	female
IOP	intraocular pressure
IPFS	initial parafoveal scotoma
M	male
MD	mean deviation
MOPP	mean ocular perfusion pressure
MVZ	macular vulnerability zone
OR	odds ratio
PLR	pointwise linear regression

PSD	pattern standard deviation
RGC	retinal ganglion cell
RNFL	retinal nerve fiber layer
VF	visual field
VRQoL	vision-related quality of life

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Synopsis

Eyes with disc hemorrhages (DH) had faster 10-2 visual field loss than those without DH.

Central visual field monitoring with 10-2 field should be considered as complementary to 24-2 field testing in eyes with DH.

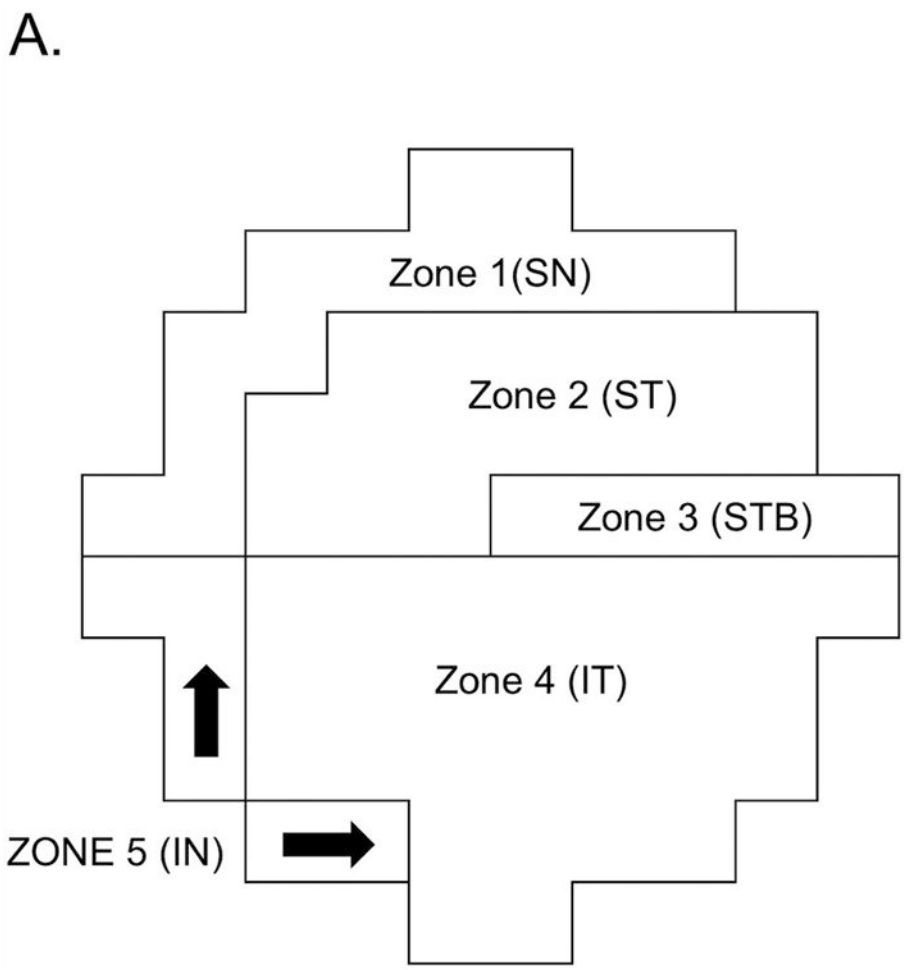

Figure 1.

Visual field zones of 10-2 VF devised by Hood et al.[13] Note that this map assumed 5 distinct VF zones based on their vulnerability to damage in the macula. Zone 1 = superior nasal zone, Zone 2 = superior temporal zone, Zone 3 = superior temporal band, Zone 4 = inferior temporal zone, Zone 5 = inferior nasal zone.

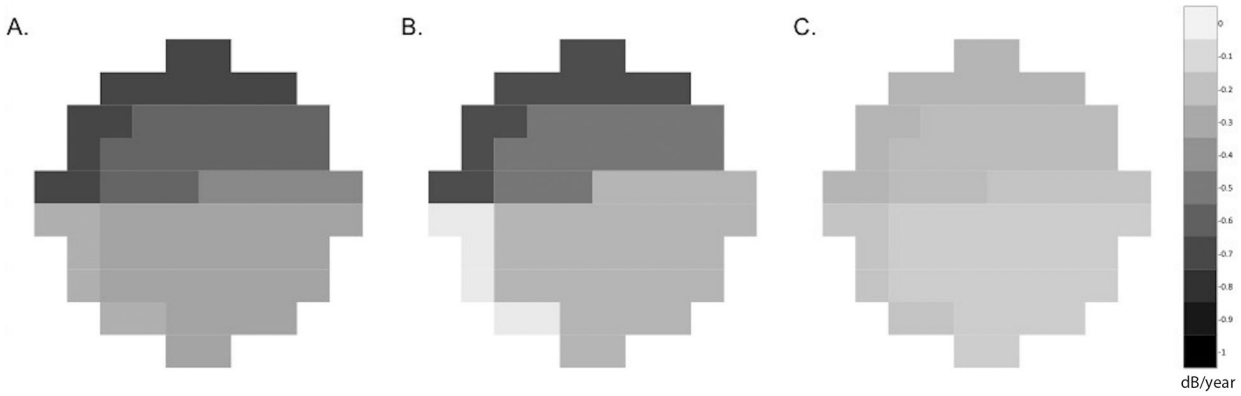

Figure 2.

Diagrams showing distributions of the mean rates of 10-2 mean deviation (MD) loss for A. DH eyes, B. Inferior DH eyes and C. Non-DH eyes. DH eyes had a faster rate of 10-2 MD loss compared to non-DH eyes. Both DH and non-DH eyes presented with a faster rate of deterioration in the superior hemifield with preservation of the superior temporal band. VFs were plotted in right eye format. Data are presented as the mean MD change rate (dB/year).

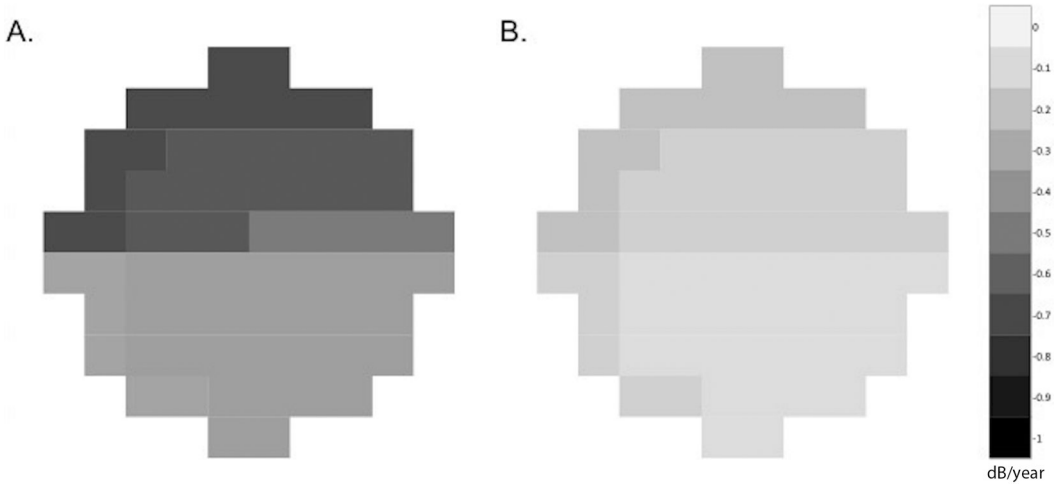

Figure 3.

Diagrams showing distributions of the mean rates of 10-2 mean deviation (MD) loss for A. DH eyes and B. Non-DH eyes in early glaucoma (MD 24-2>−6dB). The mean rate of 10-2 MD loss between DH and non-DH eyes in early glaucoma were significantly faster for both superior and inferior hemifields. VFs were plotted in right eye format. Data are presented as the mean MD change rate(dB/year).

Table 1.

Demographics and Baseline Characteristics of DH and Non-DH Eyes

Variables	DH group	Non-DH group	*P* value
By Subject (No.)	34	186	
Age (years)	71.1 (67.8, 74.5)	68.1 (66.7, 69.5)	0.089
Gender (M/F)	12/22	91/95	0.143
Race			
African American/ Non-African American	5/29	72/114	**0.007**
Self-reported HTN, n (%)	22 (64.7%)	121 (65.1%)	0.969
Self-reported DM, n (%)	3 (8.8%)	28 (15.1%)	0.337
Systolic blood pressure (mmHg)	131.8 (125.9, 137.6)	132.0 (129.2, 134.7)	0.818
Diastolic blood pressure (mmHg)	76.8 (73.3, 80.2)	78.5 (76.9, 80.2)	0.349
By Eye (No.)	39	304	
MOPP (mmHg)	54.4 (51.8, 57.0)	54.4 (53.5, 55.4)	0.994
Axial length (mm)	24.3 (23.9, 24.7)	24.2 (24.0, 24.3)	0.646
CCT (μm)	533.3 (518.8, 547.7)	537.8 (531.7, 543.9)	0.557
Baseline IOP (mmHg)	13.5 (12.4, 14.6)	14.6 (14.1, 15.1)	0.076
Mean IOP during follow-up (mmHg)	13.8 (12.8, 14.9)	14.4 (14.0, 14.9)	0.280
Diagnosis			0.145
Glaucoma suspect, Eye No. (%)	7 (18.0%)	89 (29.3%)	
Mild glaucoma, Eye No. (%)	25 (64.0%)	145 (47.7%)	
Moderate/ advanced glaucoma, Eye No. (%)	7 (18.0%)	70 (23.0%)	
Total DH No.			
Multiple DH, Eye No. (%)	18 (46.2%)		
DH Location			
Inferior, Eye No. (%)	28 (71.8%)		
Superior, Eye No. (%)	4 (10.3%)		
Both hemispheres, Eye No. (%)	7 (17.9%)		
Baseline 24-2 MD (dB)	−4.2 (−5.8, −2.7)	−4.4 (−5.1, −3.7)	0.867
Baseline 24-2 PSD (dB)	5.6 (4.3, 6.9)	4.7 (4.3, 5.2)	0.168
Baseline 10-2 MD (dB)	−3.9 (−5.5, −2.4)	−3.8 (−4.4, −3.1)	0.825
Baseline 10-2 PSD (dB)	5.2 (3.6, 6.8)	4.1 (3.6, 4.6)	0.183
Follow-up (years)	5.1 (4.9, 5.2)	5.3 (5.2, 5.5)	0.082
Visits of 24-2 Visual Field, n	7.9 (7.2, 8.7)	7.7 (7.4, 8.0)	0.212
Visits of 10-2 Visual Field, n	7.8 (7.2, 8.5)	7.6 (7.3, 7.8)	0.497

CCT = central corneal thickness; DH = disc hemorrhage; DM = diabetes mellitus; F = female; HTN = hypertension; IOP = intraocular pressure; M = male; MD = mean deviation; MOPP = mean ocular perfusion pressure; PSD = pattern standard deviation. Values are shown in mean (95% confidence interval), unless otherwise indicated. Statistically significant *P* value is shown in bold.

Table 2.

Comparison of Rates of VF Loss between DH and Non-DH Eyes

	DH Group Mean (95% CI)	Non-DH Group Mean (95% CI)	Difference Mean (95% CI)	*P* value (adjusted)
No. of Eyes	39	304		
24-2 MD Change Rate (dB/year)				
Global 24-2	−0.38 (−0.54, −0.21)	−0.21 (−0.27, −0.15)	−0.17 (−0.34, 0.01)	0.060 (0.112)
Central MD Change Rate (dB/year)				
Global 10-2	−0.50 (−0.68, −0.33)	−0.15 (−0.21, −0.09)	−0.36 (−0.54, −0.18)	**<0.001 (<0.001)**
Central Hemifield MD Change Rate (dB/year)				
Superior	−0.48 (−0.65, −0.30)	−0.16 (−0.23, −0.10)	−0.31 (−0.50, −0.12)	**0.001 (0.001)**
Inferior	−0.32 (−0.49, −0.16)	−0.14 (−0.2, −0.08)	−0.18 (−0.36, −0.01)	**0.037 (0.033)**

DH = disc hemorrhage; MD = mean deviation; VF = visual field. Values are shown in mean (95% confidence interval), unless otherwise indicated. *P* values were adjusted for age and baseline 24-2 MD. Statistically significant *P* values are shown in bold.

Table 3.

Factors Contributing to the Rate of 10-2 VF Loss Over Time in Study Participants by Univariable and Multivariable Mixed Model Analysis

Variables	Univariable Model		Multivariable Model	
	β, 95 % CI	***P* value**	**β, 95 % CI**	***P* value**
Age, per 10 year older	−0.03 (−0.09, 0.03)	0.343	−0.05 (−0.12, 0.01)	0.105
Gender: M/F	−0.05 (−0.17, 0.07)	0.437		
Race: African American/ Non-African American	−0.07 (−0.20, 0.05)	0.246		
Axial length, per 1mm longer	−0.03 (−0.08, 0.02)	0.202		
CCT, per 10 μm thinner	0.04 (−0.11, 0.20)	0.574		
Self-reported diabetes	0.07 (−0.10, 0.24)	0.423		
Self-reported hypertension	0.11 (−0.01, 0.24)	**0.068**	0.12 (0.00, 0.24)	0.051
MOPP, per 1 mmHg higher	0.00 (−0.01, 0.01)	0.592		
Baseline IOP, per 1 mmHg higher	−0.01 (−0.02, 0.01)	0.294		
Mean IOP, per 1 mmHg higher	0.00 (−0.02, 0.02)	0.935	−0.01 (−0.03, 0.00)	0.158
History of disc hemorrhage	−0.36 (−0.54, −0.18)	**<0.001**	−0.36 (−0.53, −0.18)	**<0.001**
Baseline MD 10-2, per 1 dB worse	−0.01 (−0.02, 0.00)	**0.028**		
Baseline MD 24-2, per 1 dB worse	−0.02 (−0.03, −0.01)	**<0.001**	−0.02 (−0.03, −0.01)	**<0.001**
Follow-up time, per 1 year longer	−0.04 (−0.08, 0.00)	**0.051**	−0.03 (−0.07, 0.01)	0.123

CCT = central corneal thickness; F = female; IOP = intraocular pressure; M = male; MD = mean deviation; MOPP = mean ocular perfusion pressure; VF = visual field. Age, mean IOP and variables with a P value of less than 0.10 in the univariable analysis were included in the multivariable model. Statistically significant *P* values are shown in bold.

Table 4.

Factors Contributing to the 10-2 VF Loss Progression Assessed by clustered PLR in Study Participants using Univariable and Multivariable Logistic Regression Analyses.

Variables	Univariate Model		Multivariable Model I		Multivariable Model II	
	Odds ratio, 95% CI	*P* value	Odds ratio, 95 % CI	*P* value	Odds ratio, 95 % CI	*P* value
Age, per 10 year older	10.06 (9.70, 10.44)	0.732	10.17 (9.78, 10.57)	0.404	10.18 (9.79, 10.59)	0.377
Gender: M/F	0.99 (0.48, 2.02)	0.973				
Race: African American/ Non-African American	1.38 (0.63, 3.00)	0.417				
Axial length, per 1mm longer	1.05 (0.81, 1.36)	0.719				
CCT, per 10 μm thinner	10.01 (9.93, 10.1)	0.749				
Self-reported diabetes	1.39 (0.51, 3.83)	0.519				
Self-reported hypertension	0.59 (0.28, 1.22)	0.153				
MOPP, per 1 mmHg higher	1.01 (0.96, 1.06)	0.788				
Baseline IOP, per 1 mmHg higher	1.01 (0.92, 1.10)	0.884				
Mean IOP, per 1 mmHg higher	1.01 (0.91, 1.12)	0.899	1.05 (0.95, 1.17)	0.301	1.04 (0.93, 1.15)	0.512
History of disc hemorrhage	3.65 (1.58, 8.42)	**0.002**	3.78 (1.56, 9.13)	**0.003**	3.51 (1.48, 8.29)	**0.004**
Baseline MD 10-2, per 1 dB worse	1.04 (0.99, 1.09)	**0.096**			1.05 (1, 1.11)	0.074
Baseline MD 24-2, per 1 dB worse	1.06 (1.02, 1.11)	**0.004**	1.08 (1.03, 1.13)	**0.002**		
Follow-up time, per 1 year longer	1.16 (0.98, 1.37)	**0.088**	1.17 (0.97, 1.40)	0.106	1.19 (0.97, 1.45)	0.096

CCT = central corneal thickness; F = female; IOP = intraocular pressure; M = male; MD = mean deviation; MOPP = mean ocular perfusion pressure; VF = visual field. Values are shown in odds ratio (95% confidence interval), unless otherwise indicated. Age, mean IOP and variables with a P value of less than 0.10 in the univariable analysis were included in the multivariable model. Statistically significant *P* values are shown in bold.

Table 5.

Comparison of Rates of Regional 10-2 MD Loss between DH and Non-DH Eyes

	DH Group Mean (95% CI)	Non-DH Group Mean (95% CI)	Difference Mean (95% CI)	*P* value (adjusted)
No. of Eyes	39	304		
Zonal MD Change Rate (dB/year)				
Zone 1 (superior nasal)	−0.58 (−0.79, −0.37)	−0.20 (−0.27, −0.12)	−0.39 (−0.61, −0.16)	**0.001 (<0.001)**
Zone 2 (superior temporal)	−0.71 (−0.96, −0.46)	−0.24 (−0.34, −0.15)	−0.47 (−0.73, −0.20)	**0.001 (<0.001)**
Zone 3 (superior temporal band)	−0.43 (−0.67, −0.20)	−0.18 (−0.26, −0.09)	−0.25 (−0.50, 0.00)	**0.047 (0.039)**
Zone 4 (inferior temporal)	−0.27 (−0.50, −0.04)	−0.20 (−0.28, −0.11)	−0.07 (−0.32, 0.18)	0.572 (0.527)
Zone 5 (inferior nasal)	−0.32 (−0.49, −0.16)	−0.14 (−0.20, −0.08)	−0.19 (−0.37, −0.01)	**0.042 (0.038)**

DH = disc hemorrhage; MD = mean deviation. Values are shown in mean (95% confidence interval), unless otherwise indicated.

P values were adjusted for age and baseline 24-2 MD. Statistically significant *P* values are shown in bold.