Spatially Consistent, Localized Visual Field Loss before and after Disc Hemorrhage

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PURPOSE. To evaluate the rate and location of visual field (VF) progression before and after detection of disc hemorrhage (DH).

METHODS. Disc photographs of consecutive patients with glaucoma with ≥5 SITA-Standard 24-2 VF in either eye were evaluated for the presence and location of DH. Exclusion criteria included disorders other than glaucoma likely to affect the VF and an insufficient number of VF test results to create a slope before or after DH detection. Automated pointwise linear regression was used to calculate global and localized rates of progression before and after DH.

RESULTS. One hundred sixty-eight DHs were identified in 122 patients (mean age, 68.9 ± 11.2 years). The mean number of VF tests was 9.0 ± 4.4, spanning a mean of 6.7 ± 3.8 years. Mean global progression rates before and after DH were −0.6 ± 0.8 and −1.0 ± 1.2 dB/y, respectively (P = 0.01). The mean rate of progression points corresponding to the DH sector before and after detection were −2.02 ± 1.0 and −3.7 ± 3.6 dB/y, respectively (P < 0.01). All rates were significantly faster than in fellow, non-DH eyes (P < 0.05). The VF sector with the fastest progression rate predicted the location of the future DH in 85% of cases. After the detection of DH, the same VF sector maintained the fastest progression rate in almost all eyes (92%).

CONCLUSIONS. Spatially consistent, localized VF change occurred in regions of subsequent DH and continued to progress in the same regions at a faster rate. This finding suggests that rapid, localized disease progression predisposes to DH and that progressive VF loss continues because of the ongoing damage at or adjacent to this location. (Invest Ophthalmol Vis Sci. 2009;50:4727–4735) DOI:10.1167/iovs.09-3446

A disc hemorrhage (DH) is a clinical feature of glaucoma and a strong predictor of the onset or progression of visual field (VF) loss.1 DHs typically appear as splinterlike or flame-shaped areas of bleeding within the retinal nerve fiber layer (RNFL) or optic disc neuroretinal rim.2-6 They are usually, but not always, contiguous with the disc edge or adjacent to an area of neuroretinal rim notching or RNFL defect and often occur in a region of parapapillary atrophy.7 They are missed during clinical examination in as many as 84% of cases.8 This high rate is particularly important because enhanced therapy and/or disease surveillance is warranted for these eyes because of the increased risk of progressive functional and structural loss after DH.1-6

Since the first DH description almost 100 years ago,9,10 various theories have been postulated to explain the genesis of DH and its relationship to glaucoma progression.11-14 Because DH is often undetected, and there is currently no way to predict when and which optic discs will manifest them, there has been little published information regarding longitudinal temporal and spatial associations between DH and VF loss in glaucoma. Most emphasis in the medical literature focuses on VF deterioration after DH, and very little is known about functional loss before their onset. With the advent of pointwise linear regression (PLR), it is now possible to determine rates of VF progression by points, sectors, and globally at any time point, such as the occurrence of DH, as a reference.15-19 As various cross-sectional analyses suggest that VF defects significantly correlate with localized structural damage in glaucoma,20-23 PLR analysis of the VF could help better the understanding of the functional and structural changes surrounding the onset of DH. We designed this study to evaluate global and localized rates of progression before and after the onset of DH, as well as to determine whether a correlation exists between past VF loss, DH, and future progression.

METHODS

All 43,660 consecutive subjects (132,512 VF tests) evaluated in the glaucoma referral practice of the authors (JML, CT, RR) from January 1999 to December 2008 were enrolled. The study was approved by the New York Eye and Ear Infirmary Institutional Review Board and adhered to the tenets of the Declaration of Helsinki.

After an initial visit that consisted of a complete ophthalmic examination, perimeter (24-2 SITA-SAP, HFA II; Carl Zeiss Meditec, Inc., Dublin, CA), and optic disc stereophotographs, patients were re-examined, usually at 3- to 6-month intervals, and the same tests repeated within 6 to 12 months. Subjects with five or more VF tests in both eyes were included. All disc photographs were then reviewed simultaneously by two glaucoma specialists (CGVDM, TSP) who searched for DH using a slide projector. A DH was defined as a splinterlike or flame-shaped hemorrhage on or within the RNFL or neuroretinal rim. If peripheral to the disc margin, it needed to be contiguous with the β-zone parapapillary atrophy when this feature was present.5 In cases in which the investigators disagreed, the impression of a third investigator (JML) was used for adjudication. The DH time point used in all the analyses was based on the date of the disc photograph documenting the hemorrhage. The presence of localized RNFL or neuroretinal rim loss at the site of the DH was also recorded.

Disc photographs were projected on the template developed by Garway-Heath24 to map the location of the hemorrhage on the optic disc.
results of all subsequent available VF tests were included in the analysis. The presence of at least three contiguous test points within the same optic disc sector (Fig. 1). For each detected DH, six possible optic disc sectors were designated: temporal (311–40°), superotemporal (41–80°), supronasal (81–120°), nasal (121–230°), inferonasal (231–270°), and inferotemporal (271–310°). Eyes with diabetic retinopathy, vascular occlusion, optic disc drusen, ocular trauma, and history of recent posterior vitreous detachment were excluded.

A glaucomatous VF was defined as a glaucoma hemifield test (GHT) outside normal limits on at least two consecutive baseline VF tests and the presence of at least three contiguous test points within the same hemifield on the PSD plot at P < 0.1%, with at least one at P < 0.5%, excluding points on the edge of the field or those directly above and below the blind spot. The two baseline tests required reliability indices better than 25% to be included. Data from both eyes were included as we also aimed to compare rates with fellow non-DH eyes used as the control. If an eye developed recurrent DH, the slopes were calculated by using the date of the first hemorrhage.

Automated pointwise linear regression (PLR) analysis was performed (Progressor software; ver. 3.3; Medisoft, Inc., London, UK), providing slopes (decibels/year) of progression both globally and locally for each point based on threshold maps, as well as its level of significance (probabilities).15 A Gaussian filter (based on a 3 × 3 test point grid) was also applied, to reduce measurement variability; thus, results of all subsequent available VF tests were included in the analysis irrespective of reliability criteria.15 For patients unfamiliar with automated perimetry (≤2 previous VF tests), the first two VF examinations were not included in the regression. Progression was defined as the presence of a test point with a slope of sensitivity over time >1.0 dB loss/year (P < 0.01). For edge points, a stricter slope criterion of >2 dB loss/year (also with P < 0.01) was used.15–17 The software provides an automated location of points with significant slopes of progression, which was compared with Garway-Heath mapping (Fig. 2). The progression rate for each sector was calculated by averaging the rate of significantly progressing points.

Patients were divided into three groups. Group A had ≥5 VF tests before the DH, group B had ≥5 VF tests after the DH, and group C had ≥5 VF tests both before and after the DH. The eyes in group C were therefore also members of groups A and B. A minimum of five VF tests was chosen because this is the minimum number of tests necessary to detect progression with 80% statistical power in a population with moderate VF variability (2 × SD of the MD).25

Patient age, central corneal thickness (CCT), and mean deviation (MD) value of each eye on the date of the documented DH were used for comparisons between groups. The mean intraocular pressure (IOP) within 1 year before and after the documented DH was recorded. We chose this 1-year period to better describe the IOP profile at which the hemorrhage occurred, and also to verify whether there was IOP reduction in the period after its onset.

**Statistical Analysis**

Independent categorical variables were compared using the χ² test, whereas paired analyses were performed using McNemar’s test. An independent-samples t-test was used to compare continuous variables between groups. For the group of patients with ≥5 VF before and after the DH (group C) and for comparisons between DH eyes and their fellow control eyes, paired-samples, two-tailed t-tests were used to compare the slopes of progression before and after the DH time point. Progression rates between groups A and B were compared by independent-samples t-test. Logistic regression analysis expressed as odds ratios (ORs) was used to evaluate the association between rates of progression and the occurrence of DH as a binary outcome (yes/no).

Statistical significance was considered at P < 0.05. Computerized analysis was performed with commercial software (MedCalc; MedCalc, Inc., Mariakerke, Belgium).

**RESULTS**

DHs were found in 146 eyes of 122 patients (mean age, 68.9 ± 11.2 years) among the 2051 patients with ≥5 VF. A total of 168 hemorrhages were found, which corresponded either to one or more hemorrhages detected at the time of a single disc photograph, or to recurrence. Most patients were women (58.6%) and of European ancestry (91%). The mean number of VF tests was 9.0 ± 4.4, spanning a mean of 6.7 ± 3.8 years. Most DHs (63%) occurred in the inferotemporal sector, followed by those in the superotemporal (13%) and the temporal (12%) sectors. Localized RNFL or neuroretinal rim loss was present in the same sector as the DH in 90% (132/146) of hemorrhagic discs. There were 79 eyes in group A and 89 eyes in group B. Group C comprised 22 eyes from groups A and B that had ≥5 VF tests before and after the DH. Ninety-eight patients had a single, unilateral DH. The need for adjudication by a third, masked photograph reviewer occurred three times.

Groups A and B did not show any significant difference regarding age, MD, and CCT. Considering all enrolled eyes, the mean IOP within 1 year of follow-up decreased significantly from 16.2 ± 4.0 to 14.8 ± 3.0 mm Hg (P < 0.01, paired t-test).

Tables 1 and 2 summarize the characteristics and longitudinal progression of the disc hemorrhage (black arrow) and the significantly progressing points with the Garway-Heath map (red arrows).
data from each group. There was no significant difference between groups A and B regarding follow-up time, number of disc photographs taken or VF tests performed.

**Progression before and after DH**

Mean global progression rates before and after DH were −0.6 ± 0.8 (group A) and −1.0 ± 1.2 dB/y (group B), respectively (P = 0.01). Mean localized VF progression rates for the corresponding DH sector were −2.0 ± 1.0 dB/y before the DH and 3.7 ± 3.6 dB/y after it (P < 0.01; Fig. 3).

Before DH, 46 (58%) of 79 group A eyes demonstrated significant progression. In 39 (89%) of these eyes, the DH developed in the VF sector with the fastest significant progression rate. When the adjacent VF sectors were included, the agreement increased to 43 (93%) of 46. After DH (group B), 70 (78%) 89 eyes exhibited significant VF progression. The most rapid localized VF progression corresponded to the region of the DH in 65 (92%) of 70 eyes, which increased to 100% when the adjacent VF sectors were included (Table 3).

**Progression before and after DH in the Same Eye**

For eyes with at least 5 VF before and after the DH (group C), global progression rates were faster after the DH (−0.6 ± 0.8 vs. −1.3 ± 1.2 dB/y; P = 0.01). Localized progression corresponding to the DH sector was −2.7 ± 1.1 dB/y before the DH, which increased to −4.0 ± 3.5 dB/y after it (P < 0.01; Fig. 4).

Significant VF progression occurred in 12 (54%) of 22 eyes before the DH. In 10 (83%) of 12 eyes with significant progression before the DH, the VF sector with significant progression correlated with the optic disc location of the future DH. After the DH, 18 (82%) of 22 eyes showed significant progression. The VF sector corresponding to the location of the DH had a significant slope in 17 (94%) of 18 of these eyes, which increased to 100% when the adjacent VF sectors were included (Table 4).

**Association between rates of Progression and Occurrence of DH**

DHSs in the inferotemporal sector were followed by the fastest global and localized rates of progression (−2.8 ± 1.2 dB/y before and 100% when the adjacent VF sectors were included (Table 3).

**Table 1. Characteristics of Group A and Group B**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>P*</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>68.4 ± 11.0</td>
<td>68.5 ± 10.7</td>
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<tr>
<td>Mean baseline MD (dB)</td>
<td>−6.1 ± 5.2</td>
<td>−5.8 ± 6.3</td>
</tr>
<tr>
<td>Mean CCT (µm)</td>
<td>549.4 ± 43.8</td>
<td>543.6 ± 42.2</td>
</tr>
<tr>
<td>Mean follow-up time (y)</td>
<td>6.0 ± 2.1</td>
<td>5.4 ± 2.4</td>
</tr>
<tr>
<td>Mean number of 24-2 SITA visual fields</td>
<td>8.0 ± 2.4</td>
<td>7.3 ± 2.6</td>
</tr>
<tr>
<td>Mean disc photographs reviewed (n)</td>
<td>5.9 ± 2.5</td>
<td>5.4 ± 2.7</td>
</tr>
</tbody>
</table>

* Independent-samples t-test.

**Table 2. Longitudinal Characteristics of Group C**

<table>
<thead>
<tr>
<th></th>
<th>Before DH</th>
<th>After DH</th>
<th>P*</th>
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<tbody>
<tr>
<td>Mean follow-up time (y)</td>
<td>4.8 ± 1.7</td>
<td>3.4 ± 2.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean number of 24-2 SITA visual fields</td>
<td>7.9 ± 3.0</td>
<td>8.1 ± 3.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean disc photographs reviewed (n)</td>
<td>4.6 ± 1.5</td>
<td>4.0 ± 2.1</td>
<td>0.35</td>
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</tbody>
</table>

* Paired-samples t-test.

**Table 3. Incidence of Significant Progression among DH Eyes and Association between Fastest Progressing VF Sector and Location of the DH**

<table>
<thead>
<tr>
<th></th>
<th>Before DH (Group A)</th>
<th>After DH (Group B)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes with VF progression</td>
<td>46/79 (58)</td>
<td>70/89 (78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fastest VF progression</td>
<td>39/46 (85)</td>
<td>65/70 (92)</td>
<td>0.27</td>
</tr>
<tr>
<td>in sector corresponding to DH sector</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fastest VF progression</td>
<td>43/46 (93)</td>
<td>70/70 (100)</td>
<td>0.30</td>
</tr>
<tr>
<td>in sector corresponding to DH sector (including adjacent VF sectors)</td>
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Data are number of progressors/total number in group (%).
loss is a significant predictor of the occurrence of DH.\textsuperscript{27} This observation supports our finding that 90\% of DH occurred in areas of localized rim notching. This characteristic was found in several other studies\textsuperscript{28–31} and supports the premise that ultrastructural features within areas of notching may ultimately lead to hemorrhage. We confirmed previous reports of the association between DH and future localized progression.\textsuperscript{32–34} and assessed the local and global rates of progression for these eyes.

Our data demonstrate that rapid, progressive, localized functional loss occurs most often in the area in which the future DH will occur. Law et al.\textsuperscript{35} evaluated a series of disc photographs preceding the onset of DH and found that among eyes that later developed DH, 100\% had preexisting neural rim notches that antedated the occurrence of the DH by a median of 21.5 months. The authors also speculated that a neural rim notch and DH may be different presentations of an underlying degenerative process corresponding to a localized geographic area of the optic disc and its surroundings. Jeoung et al.\textsuperscript{31} showed that significant RNFL loss using optical coherence tomography was already present in DH eyes with apparently normal RNFL configuration by fundus photography, indicating that a damaged RNFL, despite normal achromatic perimeter, was already present.

Given these prior reports and our findings of spatially congruous, rapid, localized, functional progression before DH, it appears likely that more rapid disease progression (i.e., a relatively rapid progressive neurodegeneration) leads to DH. In our study, each 1\,dB/y increase in the progression rate within a VF sector increased the chance of developing a DH by 47\%, whereas a localized rate of progression \( \geq 3.0 \, \text{dB/y} \) increased the risk of DH by 65\%. Our data support the hypothesis that local DH develops because of an ongoing degeneration of rim architecture (neural tissue+extracellular matrix+vessels), causing an abrupt rupture of the microvasculature. VF loss continues because of the ongoing structural damage at or adjacent to this location and is consistent with the usual clinical appearance of a DH at the edge of an existing RNFL or neuroretinal defect (Fig. 5). Slower disease progression (and therefore slower functional and structural injury) is less likely to be associated with DH because of the slower rate of localized progressive neurodegeneration.

The rates of VF loss in DH eyes were, on average, twice as fast as their fellow, non-DH eyes. This finding is particularly relevant, as it shows that these eyes are not only likely to progress in the future, but should also alert the clinician that treatment until that moment may have been suboptimal. The Early Manifest Glaucoma Trial (EMGT)\textsuperscript{26} suggested that DH cannot be considered an indication of insufficient IOP-lowering treatment, and that glaucoma progression in eyes with DH cannot be totally halted by IOP reduction. The fact that the authors found that IOP-reducing treatment was unrelated to the presence or frequency of DH could indicate that treatment

\begin{table}[h]
\centering
\caption{Incidence of Significant Progression among DH Eyes and Association between Fastest Progressing VF Sector and Location of the DH in Group C}
\begin{tabular}{|c|c|c|c|}
\hline
 & Before DH & After DH & \( P \) \\
\hline
Eyes with VF progression & 12/22 (54) & 18/22 (82) & 0.10 \\
Fastest VF progression in sector corresponding to DH sector & 10/12 (83) & 17/18 (94) & 0.70 \\
Fastest VF progression in sector corresponding to DH sector (including adjacent VF sectors) & 10/12 (83) & 18/18 (100) & 0.30 \\
\hline
\end{tabular}
\end{table}
goal in that study may have been insufficient to slow VF progression before the onset of the DH. On the other hand, Miyake et al.\textsuperscript{35} showed that the cumulative probability of detecting a DH significantly decreased after trabeculectomy. The more aggressive IOP reduction obtained surgically is likely to be more effective in slowing rates of progression,\textsuperscript{36} which may ultimately prevent the degeneration of disc neuroretinal tissue. Moreover, the OHTS found an increased cumulative incidence of DH after a glaucoma end point was reached (0.5\%-2.5\% per year).\textsuperscript{8} As we demonstrated, DH eyes already have faster rates of progression than fellow, non-DH eyes before the onset of the DH, which subsequently increased after its occurrence. Our results agree with the findings of the OHTS and are consistent with localized progression even before the DH were detected. Even though we did not evaluate the role of IOP reduction on the rates of progression after DH in this study, given that IOP is the main risk factor for glaucoma development and progression, there is strong evidence that eyes with lower IOP are more likely to progress more slowly than those with higher IOP.\textsuperscript{37-40}

We also observed that the correlation between DH and past or future progression depended on its location. Hemorrhages in nasal optic disc sectors were associated with slightly slower progression rates and showed poor topographic agreement with VF progression. Other studies investigating structure and function correlations in glaucoma have also shown weaker correlations between those sectors and VF loss.\textsuperscript{22-25} A possible explanation is that the Garway-Heath map and a 24-2 strategy resulted in worse representation of peripheral retinal areas that are not tested with conventional static perimetry. Moreover, the nasal optic disc sector corresponds to 110°, or approximately 30\% of its circumference. The corresponding VF sector contains only four points, or 7\% of the points of a 24-2 test (Fig. 1). It is possible that if remote areas of the retina could be tested and plotted in a map, we could have found faster rates and better agreement for the nasal sectors. However, since standard achromatic perimetry remains the best method of assessing visual function in a clinical basis,\textsuperscript{41,42} the finding of DH in the nasal sectors of the disc has low association with past or future field loss, as assessed by conventional perimetry.

The limitations of our study are its retrospective nature and the relatively low frequency of optic disc documentation (once per year), which may have lead to underestimation of the true incidence of DH in our sample. In the EMGT,\textsuperscript{26} for instance, all patients were seen every 3 months and were photographed twice a year, which resulted in a much higher incidence of DH (55\%) than our study. Hence, one could argue that the fast progression rates observed in our study before DH could be
due to previously undetected hemorrhages, as most recurrences tend to occur close to previous ones.17 We tried to minimize this effect by enrolling only the first detected DH of each eye in cases of recurrence. We maximized the likelihood of detecting DH by choosing a population undergoing repeated optic disc photography and perimeter and by performing masked review of disc photographs.18 Similar to group B, eyes in group A were followed for a mean of 6 years before the onset of DH and underwent photography once per year, on average (Table 1). The use of the fellow, non-DH eyes as a control group allowed us to demonstrate that the progression rates before DH were significantly greater in the DH eyes. We used fellow eyes as controls to (1) match the groups for sex, race, age, type of glaucoma; (2) eliminate the bias that could be introduced by differences between the groups with respect to systemic factors that could be implicated in the development of DH; (3) maintain parity in the number of VF and disc photographs to keep the chance of finding a DH roughly the same; and (4) permit use of a paired statistical analysis. It is possible, or even likely, that we may have missed some DH that occurred during the intervals between photographs in our study or that a DH, before the beginning of our study, was followed by later, fast progression. These possibilities notwithstanding, the DH identified as the DH reference for groups A and B invariably occurred in the region of most rapid localized VF progression and that in group C this was true both before and after the hemorrhage. Ideally, a prospective longitudinal study with disc photographs performed at much more frequent intervals would give a better estimation of the true incidence of DH in a treated glaucoma population. The findings of the present study suggest that clinicians may want to increase surveillance of patients undergoing rapid localized progression and focus diagnostic resources (such as disc photography) on these individuals on a more frequent basis.

Our results suggest that rapid, localized, spatially consistent, VF progression occurs before and after DH. This supports the hypothesis that DH results from an ongoing structural degeneration of the neuroretinal rim, rather than a primary vascular pathologic process11,12 that subsequently leads, de novo, to further structural and functional injury. Restated, the glaucomatous damage to the optic nerve occurs before and after DH and appears to be independent of it. Eyes with slower rates of change may develop fewer DHs, because the degeneration of rim tissue is correspondingly slower and produces less frequent vascular rupture. The rapid structural and functional progression after DH continues at the same or adjacent location after its resolution and provides evidence that the microvascular disruption that results in bleeding is the result of a structural degeneration rather than a cause of glaucoma progression in and of itself, as there were very few eyes that developed a DH without evidence of prior, rapid, corresponding, localized functional injury. In addition, a rapid, localized rate of progression was a good predictor of the location of a future DH and continued field loss in glaucomatous eyes. Lastly, our results demonstrate that a DH should be viewed not only as a risk factor for future progression, but also as evidence and confirmation of past, localized progression. Consideration should be given to the inclusion of DH as a structural endpoint consistent with glaucoma progression in future glaucoma clinical trials.

In conclusion, spatially consistent, localized VF loss precedes the onset of DH in glaucomatous eyes. DH most often occurs in the region of most rapid glaucoma progression and is associated with future sustained and accelerated functional loss in these eyes.

References


