Diffuse Loss of Sensitivity in Early Glaucoma

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PURPOSE. To establish whether there is significant diffuse loss of sensitivity in a population of patients with early glaucoma.

METHODS. The differential light sensitivities at the 10 most sensitive locations from within the central 24° of program 30-2 of the Humphrey Field Analyzer (Humphrey Instruments, San Leandro, CA) were compared in 38 pairs of age-matched subjects, one of each pair with early primary open-angle glaucoma (POAG) and the other with normal eyes. All subjects had had experience with automated perimetry and had clear media, visual acuity of 20/25 or better, and one or fewer false-positive or false-negative responses to catch trials.

RESULTS. The mean difference in age between the subjects with glaucoma and normal subjects was 29 days (P = 0.44, maximum 1.42 years). The mean paired difference in pupil size was 0.16 mm (P = 0.26), and visual acuity was higher in the glaucoma-affected subjects (P = 0.044). The 10 highest sensitivity measurements in the POAG-affected subjects were found to be lower by a median of between 1.0 and 2.0 dB than those in the normal pair members (0.0001 < P < 0.012, sign test). In 60% of the pairs the sensitivity at the seventh most sensitive location was 2 dB or more lower in the POAG-affected eyes.

CONCLUSIONS. Early glaucomatous visual field loss frequently involves a diffuse component that includes the 10 most sensitive locations. These findings suggest that purely localized visual field loss in glaucoma is rare. These observations could not be explained by factors of pupil size and media opacity. (Invest Ophtalmol Vis Sci. 1999;40:3147–3151)

Visual field loss in glaucoma has classically been divided into localized and diffuse types.1–4 Localized loss includes arcuate and paracentral defects, whereas diffuse loss is defined as a reduction in sensitivity over the whole visual field manifesting itself as either a contraction of isopters in kinetic perimetry or lowered sensitivities in static threshold perimetry. It has often been thought that these two classes of visual field loss result from different pathophysiological mechanisms,5 diffuse loss being more prevalent in cases in which the intraocular pressure (IOP) is high and localized loss being more prevalent when the IOP is normal.6–9

The existence of diffuse visual field loss in glaucoma has been brought into question by Heijl.10 From an analysis of the results of threshold perimetry he established that the 10 best points in the visual field of patients with early glaucomatous changes (localized visual field loss and/or optic nerve head changes) were not significantly different from those of a high-risk group who did not show any glaucomatous changes. Best points were defined as those with the most positive difference between measured sensitivity and age-matched normal values. He concluded that, although widespread reductions in sensitivity may be common in glaucoma, diffuse loss, extending to the best points, is rare or nonexistent. Further study by Åsman and Heijl11 supported this finding. They demonstrated, in a large sample of visual fields, that very few (3%) showed exclusive diffuse loss and that in most cases this loss could be attributed to confounding factors such as miosis and cataract.

Exclusive diffuse loss has been shown, however, to exist in a small number of patients with glaucoma.8,12 In these studies considerable effort went into excluding the confounding factors highlighted by Åsman and Heijl11 and into demonstrating that this type of loss is evident in serial visual fields.13

Most of the previous research with static threshold perimetry has concentrated on establishing whether diffuse loss exists in isolation and whether diffuse loss occurs in the earliest stages of glaucoma. Previous research has not investigated the question of whether there is significant diffuse loss in patients with early glaucomatous visual field loss nor has it determined the magnitude of the loss, if it exists. There is also concern that the previous work of Heijl10 may have been biased by the selection of a high-risk population, rather than normal subjects, for comparison with patients with glaucoma.

The purpose of this study was to establish whether there is significant diffuse loss of sensitivity in patients with early glaucoma. The analysis is based on paired comparison between age-matched early glaucomatous and normal visual fields. The differential light sensitivity at the 10 most sensitive locations, pupil size, IOP, and visual acuity were compared between the members of each pair.
METHODS

Patient Data

The analysis is based on visual fields of patients with confirmed primary open-angle glaucoma (POAG) and normal control subjects observed prospectively at the Department of Ophthalmology, Dalhousie University, Halifax, Nova Scotia. Patients were included if all the following inclusion criteria were met: diagnosis of open-angle glaucoma with characteristic glaucomatous optic disc damage, a visual field with a mean deviation (MD) index of less than 10 dB, normal open angles by gonioscopy, best corrected visual acuity 20/25 or better, and willingness to give informed consent to participate in the study. Patients were excluded if any of the following were found: concomitant ocular disease, systemic disease or systemic medication known to affect the visual field, refractive error exceeding 5 D equivalent sphere or 3 D of astigmatism, and contact lens wear. All patients with POAG were receiving medical ocular hypotensive treatment. Those taking pilocarpine did not take their medications on the day of the test.

Normal control subjects were included if all the following inclusion criteria were met: normal ocular examination, best corrected visual acuity of 20/25 or better, IOP less than 23 mm Hg, negative family history of glaucoma, and willingness to give informed consent to participate in the study. Normal subjects were excluded if any of the following were found: systemic disease or systemic medication known to affect the visual field, refractive error exceeding 5 D equivalent sphere or 3 D of astigmatism, and contact lens wear.

All analyses were based on a single test result from one randomly selected eye of each subject. All patients with POAG and normal control subjects had had experience with program 30-2 on the Humphrey Visual Field Analyzer (HFA, Humphrey Instruments, San Leandro, CA). The study was approved by the Queen Elizabeth II Health Sciences Center Research Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject.

Because frequent response errors can elevate or depress sensitivity estimates, visual fields with more than one false-positive or false-negative response to catch trials were removed from the sample. The remaining sample contained a single visual field from 46 eyes with POAG and 109 normal eyes. Adjustment for age effects, including nonglaucomatous loss in sensitivity and increased variance was achieved by selecting age-matched pairs from this population. Pairs were selected if the age difference between the normal subject and the POAG patient in each pair was less than 2 years. The selection process was based solely on age, with no account taken of the visual field data. The final sample contained 38 POAG–normal pairs.

Localized loss in the visual field can reduce the sensitivity measures at the most sensitive locations. To compensate for this effect, locations with localized loss (indicated by a pattern deviation probability value <5%) in each glaucomatous visual field were first identified. The threshold values at the corresponding locations in the visual field of the normal member of the pair were then made identical with those of the glaucoma-affected member. Each normal visual field was thereby artificially given locations of localized loss similar to that of its paired glaucomatous field.

After ranking the sensitivity values of each visual field, the 10 most sensitive locations (highest decibel value) within the central 24° of each visual field were extracted. The location of the most sensitive values did not necessarily correspond between the POAG and the normal members of each pair because of physiological differences in sensitivity profiles and random variations in threshold estimates. Sensitivity differences between the members of each pair, at each of their 10 most sensitive locations, were tested for significance with a sign test. Differences in visual acuity, IOP, and pupil sizes were also recorded for each pair.

RESULTS

The patients with POAG had early visual field loss as estimated by the global MD index (median MD = −3.1 ± 2.40 dB).

On average, the patients with POAG were 29 days older, (normal–POAG range, −1.41 to +1.42). The differences were not statistically significant (P = 0.44, Wilcoxon matched-pairs test). Pupil size was measured at the beginning of each visual field examination. The pupil diameter in the POAG-affected eye was, on average, 0.16 mm larger than that of the paired normal eye (normal–POAG range, −1 to +1). This difference did not reach statistical significance (P = 0.26, Wilcoxon matched-pairs test). The POAG-affected members had a slightly higher acuity than the normal members (P = 0.044, Wilcoxon matched-pairs test). The POAG-affected members also had higher IOPs (P < 0.0001, Wilcoxon matched-pairs test). The mean IOP for the POAG-affected members was 18.8 mm Hg (range, 12–28 mm Hg), whereas the normal subjects had a mean IOP of 15.1 mm Hg (range, 10–22 mm Hg).

The average difference in sensitivity between the POAG-affected and normal members of each pair (n = 38) is shown in Table 1 for each of the 10 most sensitive locations. The number of cases in which the normal member of each pair had a higher sensitivity than the POAG-affected member is also shown in Table 1, along with the number of cases in which the POAG-affected and normal members of each pair did not have the same sensitivity (non-ties), as well as the probability that this would occur by chance. Figure 1 shows an example, taken from the seventh most sensitive location, of the distribution of sensitivity differences for the 38 matched pairs. This distribution, which is typical in the most sensitive locations, is significantly nonnormal (Shapiro–Wilks test, P < 0.04). Non parametric statistics were used for the paired comparisons.

DISCUSSION

The data show that the patients with early POAG had significant reductions in sensitivity that extended to the most sensitive locations in the visual field. Our results suggest that diffuse loss is a common finding in eyes with POAG with 60% of matched pairs showing a 2 dB or lower sensitivity in the glaucomatous eyes at the seventh most sensitive test location, a result that supports the early work of Aulhorn and Harms.

There are a number of factors that could account for a difference in sensitivity between normal and glaucomatous eyes. The gradual loss in sensitivity with age is one. Our study compensated for this factor by using an age-matched comparison between POAG-affected and normal subjects. Another potential factor is media opacity. There are a number of reasons why this is unlikely to have affected the results of this study. First, the data came from a prospective study that ex-
cluded subjects with any clinically significant cataract based on visual acuity and clinical observation. Second, an analysis of visual acuity in the normal and POAG-affected pair members found a slightly higher visual acuity in the POAG-affected members in all pairs. Third, media changes tend to be age related and this study, by using age-matched pairs, compensated for this. Another potential factor is a difference in pupil size brought about by miotic therapy for glaucoma. Because differences in pupil size between the normal and POAG-affected members of each pair were not significant, pupil size cannot account for the sensitivity differences found in the pairs.

The normal subjects had, on average, an IOP that was 3.7 mm Hg (19%) below that of the subjects with POAG. Although large reductions in IOP (>40%) have been shown to be associated with an increase in sensitivity, measured with the global visual field MD index, smaller differences (<35%) have been reported to have no effect on this index. The IOP difference between the normal and POAG-affected subjects was small and is therefore unlikely to be the cause of the sensitivity differences found in the pairs.

Although our results agree with the earlier work of Aulhorn and Harms they do not agree with the later work of Heijl. Heijl studied a population of high-risk patients (those with high IOP in at least one eye without localized visual field loss or optic disc changes in either eye). Within this population he found 14 patients with progressive change (with development of either localized visual field or optic nerve head changes). He then compared the sum of the 10 best points (determined as sensitivity differences between the observed and age-matched values) in the group that demonstrated change with those that showed no change. There are a number of explanations of why Heijl did not find a significant difference between these groups. The first is that his analysis may have been underpowered. His data showed a difference in sensitivity at the 10 best points (determined as sensitivity differences between the observed and age-matched values) in the group that demonstrated change with those that showed no change. There are a number of explanations of why Heijl did not find a significant difference between these groups. The first is that his analysis may have been underpowered. His data showed a difference in sensitivity at the 10 best points (an average of 0.57 dB per location) but with a sample size of 14, this did not reach statistical significance (5% level) when using analysis of vari-

### Table 1. Average Difference in Sensitivity between the POAG-Affected and Normal Members of Matched Pairs

<table>
<thead>
<tr>
<th>Field Sensitivity Rank</th>
<th>Average/Median Difference*</th>
<th>Number of Non-Ties†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.16/1.0</td>
<td>23/31</td>
<td>0.0119</td>
</tr>
<tr>
<td>2</td>
<td>1.47/1.5</td>
<td>23/27</td>
<td>0.0005</td>
</tr>
<tr>
<td>3</td>
<td>1.39/1.5</td>
<td>27/33</td>
<td>0.0005</td>
</tr>
<tr>
<td>4</td>
<td>1.45/2.0</td>
<td>26/31</td>
<td>0.0003</td>
</tr>
<tr>
<td>5</td>
<td>1.61/2.0</td>
<td>27/32</td>
<td>0.0002</td>
</tr>
<tr>
<td>6</td>
<td>1.58/2.0</td>
<td>27/31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7</td>
<td>1.65/2.0</td>
<td>24/28</td>
<td>0.0003</td>
</tr>
<tr>
<td>8</td>
<td>1.68/2.0</td>
<td>25/29</td>
<td>0.0002</td>
</tr>
<tr>
<td>9</td>
<td>1.58/2.0</td>
<td>26/30</td>
<td>0.0001</td>
</tr>
<tr>
<td>10</td>
<td>1.68/2.0</td>
<td>26/30</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* In decibels, normal subject – POAG-affected subject.
† Number of cases in which pairs of normal and POAG-affected subjects did not have the same sensitivity; normal subject > POAG-affected subject.
‡ Wilcoxon matched-pairs test.

![Figure 1](http://iovs.arvojournals.org/pdfaccess.ashx?url=data/journals/iovs/932899/ on 06/24/2017)
ance. Increasing the sample size or performing a different type of statistical analysis, such as pairwise analysis, may have resulted in a significant difference between the two groups. A second explanation is that Heijl compared his early cases of glaucoma with a high-risk, rather than a normal, population. The high-risk population may have included cases with some diffuse visual field loss, thereby reducing the chances of finding a significant difference between the groups.

Heijl's study differed from this work in that it was designed to investigate whether diffuse loss occurs at the earliest stages of glaucoma rather than whether it occurs in cases with established visual field loss. Two of Heijl's glaucoma sample (N = 14) had disc changes without detectable localized visual field loss. In this study all eyes with a diagnosis of glaucoma had some visual field loss although in the majority of cases it was mild (median MD = −3.1 ± 2.4 dB). Although this study established that the sensitivity was diffusely lowered in early POAG, it has not established when this occurred. Further work is needed to establish the sequence of visual field changes and how this sequence varies within the clinical population.

Åsman and Heijl, who also concluded that diffuse loss was a rare event in POAG, based their definition of diffuse loss on the glaucoma hemifield test. Their analysis only reports diffuse loss when it occurs in isolation, not when it occurs in conjunction with localized loss. Their results are not, therefore, contrary to those of the present study that show that diffuse loss often accompanies localized loss in early glaucoma.

Localized loss can reduce the sensitivity estimates at the most sensitive locations. The amount of the reduction is dependent on the extent of the localized loss and whether it includes the most sensitive values. This effect was described by Åsman who reported an average reduction of −1.5 dB in cases in which widespread localized loss resulted in a highly significant MD value. In cases in which the loss was less severe (MD value not significantly different from normal) Åsman reported a relatively modest effect of −0.2 dB. To compensate for this effect, locations with localized loss (indicated by a pattern deviation probability value <5%) in each glaucomatous visual field were first identified. The threshold values at the corresponding locations in the visual field of the normal member of the pair was then made identical with that of the glaucoma-affected member. Each normal visual field was thereby artificially given locations of localized loss, similar to that of its paired glaucomatous field. Compensating for this potential artifact had relatively little effect on the results, which reflects the relatively early stage of glaucomatous visual field loss in the POAG-affected population (on average, only 4 of 50 locations had a pattern deviation probability value of <5%). The less than 5% level was used as a cutoff for copying to maximize the extent of localized loss. The choice of 2% or 1% levels would have reduced the extent of the localized loss and increased the already significant difference between the normal and POAG-affected eyes.

Although significant differences have been found at the most sensitive locations, the current techniques of threshold perimetry and subsequent analysis may not be very efficient at detecting diffuse loss. Although new analytical techniques may improve diffuse loss estimates, the inherent variability of the threshold estimates used in perimetry may limit their precision in estimating the extent of diffuse loss. If better techniques can be developed for the detection of diffuse loss, the combination of these with standard perimetry may lead to improvements in the early detection of glaucoma.

The finding that there is a significant amount of diffuse loss in early POAG has implications for the calculation of pattern-deviation values. Pattern-deviation values correct for variations in the height of the hill of vision by assuming that the best points are not affected in early glaucoma. In the Statpac (Humphrey Instruments, San Leandro, CA) analysis the 15 percentile in rank ordering of best points (seventh best point) is used in the calculation of pattern deviation. The frequent occurrence of diffuse loss in early POAG, which extends to the seventh best location (see Fig. 1), affects the calculation of pattern-deviation values. In the current form of Statpac analysis the pattern-deviation values are relative to the diffuse level of loss at the seventh best point.

The existence of two different types of visual field loss in glaucoma may have important implications in the pathophysiology of the disease. Several researchers have reported differences in the types of visual field loss found with high-tension and normal-tension glaucoma. Normal-tension glaucoma is associated with more focal loss and less diffuse loss than high-tension glaucoma. Although cases of pure diffuse loss have been reported it appears that these are relatively rare events and that in most cases diffuse changes occur in tandem with localized loss. The high significance levels found in this study imply that diffuse loss occurs in a large percentage of eyes with glaucoma. The data also suggest that the existence of purely localized loss is a relatively rare event.

In summary, the sensitivity of the most sensitive locations in the visual field of patients with early glaucoma visual field damage are significantly lower than those of age-matched normal subjects. This indicates that early glaucomatous visual field loss may nearly always have a diffuse component.

References
