Pattern of Early Visual Field Loss in HIV-Infected Patients

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Objective: To determine the topographic pattern of visual field loss, if any, and its relationship to the stage of disease in human immunodeficiency virus–positive patients without infectious retinopathy.

Methods: A total of 151 eyes from 81 alert and cooperative patients with human immunodeficiency virus were evaluated with visual field testing. Results were analyzed relative to the associated underlying nerve fiber layer patterns associated with retinal ganglion cell axons as they traverse the retina to the optic nerve. The stage of visual field loss was analyzed relative to the length of survival using Kaplan-Meier survival analysis.

Results: No correlation of CD4 cell count with visual field mean defect ($r^2 = 0.23$) or corrected pattern standard deviation ($r^2 = 0.00$) was found. A pattern of visual field loss, consistent with sparing of the papillomacular bundles and associated with damage primarily to the inferior retina external to the posterior pole, was found. Survival analysis indicated a significant difference in time of survival between individuals with normal visual fields and those with a diffuse visual field loss, with a trend to less survival with increasing field loss severity.

Conclusions: These results are consistent with disease at the level of the optic nerve. The relationship of stage of visual field loss to survival has important implications for early detection of field loss and appropriate therapeutic intervention to maintain function and quality of life.


Results

Ages for the HIV-positive group ranged from 22.6 to 53.7 years (mean ± SD, 38.3 ± 7.0). Three subjects were women and 78 were men. Visual fields were normal in 88 eyes, but 11 eyes had a loss detected by the mean defect only, while 32 eyes had early visual field loss and 20 had moderate visual field loss. No eyes had advanced field loss on study entry, perhaps due to our exclusion of eyes with infectious retinopathy.

Eighty-one patients were evaluated with visual field testing. Eleven patients had only 1 eye tested (3 with abnor-
SUBJECTS AND METHODS

This is a cross-sectional analysis of data from a prospective longitudinal study on the effects of HIV infection on visual function. This investigation was approved by the Human Subjects Committee at the University of California, San Diego. The nature of the procedures was fully explained, and informed consent was obtained from each subject.

SUBJECTS

The patient participants for this study were all selected from a longitudinally followed up cohort at the University of California, San Diego, HIV Neurobehavioral Research Center, and the AIDS [acquired immunodeficiency syndrome] Ocular Research Unit. As part of participation, each volunteer received extensive neuropsychologic testing and neurologic evaluations, which allowed us to screen our participants so none were classified as having HIV-related dementia. Ratings of dementia were determined by criteria established by the American Academy of Neurology AIDS Task Force and the HIV Neurobehavioral Research Center group,19,20 and were summarized previously by our group.13 A total of 81 participants (151 eyes) met the inclusion criteria for this study. CD4 cell counts were recorded for comparison with visual field. Participants were classified by Centers for Disease Control and Prevention (CDC) category, with 18 in category A, 19 in B, and 43 in C (CD4 cell count was not available for 1 subject).

OPHTHALMOLOGIC EVALUATION

Each participant was given a complete ophthalmologic examination, including indirect ophthalmoscopy and intraocular pressure measurements. We included only those patients with 20/25 (or better) normal or corrected-to-normal Snellen visual acuity using the Early Treatment Diabetic Retinopathy Self-illuminated chart, a spherical refraction within ±0.5 diopters (D) and a cylinder within ±3.0 D of plano, normal intraocular pressures (≤21 mm Hg), absence of cataract or any visible media opacity, no other degenerative retinal disease, no history of familial glaucoma, no HIV-related infectious retinopathy (eg, cytomegalovirus retinitis), and reliable visual fields. The optic discs were normal at clinical examination. In addition, no consistently seen abnormalities of the optic nerve in patients with AIDS but without retinopathy have been reported. Reliable visual fields were defined as those with less than 5% false-positives, 25% false-negatives, and 25% fixation losses; these are conservative standard cutoff values for clinical trials with this type of perimetry.21 These cutoffs helped to partially rule out fatigue or illness in patients. From 182 eyes, 31 were excluded for exceeding these limits. Patients with noninfectious HIV-related retinopathy (cotton-wool spots) were included; their retinases were photographed (60° fields) at the time of ophthalmologic examination to document the retinopathy. Only 12 (8.0%) of 151 eyes had a history of cotton-wool spots before the examination; 6 (4.0%) had a history both before and on the day of examination; and 7 (4.6%) had cotton-wool spots on the day of examination with none previously documented. However, cotton-wool spots may come and go, and after they have resolved, the retina may appear normal (see “Comment” section). All patients in this study were evaluated before the introduction of highly active antiretroviral therapies.22,23

VISUAL FIELD TESTING

Visual fields were analyzed within 2 weeks of the ophthalmologic examination. All patients were cooperative and fully understood all testing procedures. We used a Humphrey Visual Field Analyzer (model 620; Humphrey Instruments, Inc, San Leandro, Calif), program 24-2, and routine settings for evaluating visual fields. Patients had both eyes tested in randomized order (order generated by computer). Patients were given a brief rest between tests of at least 5 minutes. Patients were required to perform at least 2 visual fields on the study eye(s) on separate dates so that classification as normal or abnormal and for degree of severity was repeatable. Since patients entered the study at various stages of disease, we also analyzed the first repeatable abnormal visual field or, if none were abnormal, the first visual field. To determine the earliest pattern of field loss, visual fields were categorized by severity and analyzed as such to show the pattern found at each stage of field loss.
SCORING VISUAL FIELDS

Each visual field was scored by experts (P.A.S. and D.J.P.) independently; any conflicts were resolved by consensus. Scoring parameters were well defined, so all discrepancies were the result of errors in scoring and not disagreement. Visual fields were analyzed using the field analyzer's internal statistics program for visual field analysis, STATPAC 2.24 The values for several of this program's indices were tabulated, and each is described briefly herein. The percentile cutoffs given are those standard for identifying abnormality with STATPAC 2.

Mean defect given by the STATPAC 2 program reflects the average difference from normal for all test locations combined, excluding the fovea. This was considered abnormal if it fell outside the 95% normal limits.

The corrected pattern standard deviation (CPSD) is a measure of the shift in the shape of the visual field from normal, after correcting for short-term fluctuation within a test. It is an index of localized loss in the visual field, and was considered abnormal if it fell outside the 95% normal limits.

Short-term fluctuation is a measure of intratest variability. This was considered abnormal if it fell outside the 95% normal limit but was not used in classification of field severity as it is taken into account when computing the CPSD.

The Glaucoma Hemifield Test is a statistical analysis also designed to search for localized defects by dividing the visual field test locations into 10 sectors, 5 in the superior field and 5 corresponding ones in the inferior field. Results outside the 99.5 percentile of the Humphrey internal normative database (n > 800 eyes) were considered abnormal. This analysis also highlights fields that show an overall general depression outside the normal 99.5 percentile.

The pattern deviation plot from the STATPAC 2 printout of visual field results gives the percentile score for each test location relative to the normal database. We used this plot and recorded the total number of defective points at each percentile (5%, 2%, 1%, and 0.5%) for each field. We also recorded the number of clusters with 3 or more adjacent points defective on the pattern deviation plot and the percentile score for the fovea if defective.

To be considered abnormal, a visual field must have had a CPSD outside 95% normal limits, a Glaucoma Hemifield Test result outside the 99.5% normal limits, or a mean defect outside the 99% limits, all for age-specific norms. The field also had to show repeatable visual field loss on a second visit with at least 1 point of a cluster of 3 in the same Glaucoma Hemifield Test sector (sectors 1 and 2 were considered the same). A point was considered abnormal if it showed the 5%, 2%, 1%, or 0.5% probability value on the STATPAC 2 result.

Severity of the visual fields was also scored as normal (0), early (1), moderate (2), advanced (3), or mean defect only (4), based on a consensus definition that is currently in use in a National Eye Institute–sponsored multicenter trial (Table 1).21 For topographic field analysis, we used the perimeter nerve fiber bundle map26,27 to divide the 24° visual field into 21 zones (Figure 1). Foveal results (zone 11) were not included in this analysis. A visual field zone was defined as having reduced sensitivity if (1) more than 50% of its test points were outside the 95% normal limits or (2) more than 30% of its test points were outside the 95% normal limits with at least 1 test point outside the 99% normal limit.26,29

In summary, visual fields were classified by severity of field loss, location of field loss, and number of points affected.

ANALYSIS

Several methods of analysis were applied to these data to identify patterns associated with severity of field loss and CDC classification. Analysis of variance was used to assess differences in groups stratified by severity of field loss or by CDC classification. Correlations were assessed for nominal visual field indices of mean defect and CPSD with CD4 cell counts. Mean time of measurement of CD4 cell counts before visual field testing was −75.9 days with an SD of 112 days. The percentage of eyes in each severity group falling outside normal limits for each visual field zone was calculated. The data from both eyes, when available, were included in these analyses, but to rule out significant effects due to the increased correlation between eyes from the same individual, all analyses were repeated for a single eye (the first eye tested from each person). There were no significant differences in results between using the first tested eye only vs using both eyes when available, so results are reported for the combined eye analysis, except when comparisons of first eye tested vs second eye tested are used to assess fatigue effects. Finally, Kaplan-Meier survival analysis was used to determine the relationship of visual field severity to patient survival after testing. For this analysis, patients were classified by the eye with worse visual field grade.

Mean ± SD CPSD value for each group was 0.89 ± 0.69 dB (normal field), 2.71 ± 0.49 dB (early field loss), 4.90 ± 1.72 dB (moderate field loss), and 0.68 ± 0.79 dB (by mean defect only). There was no correlation between CPSD and CD4 cell count (r² = 0.00, P = .61) (Figure 4).

Mean numbers and SDs of points identified at the different percentile cutoffs of STATPAC 2 are shown in Table 2. The numbers within each percentile increased with increasing field severity.

Visual field testing may be fatiguing and, in HIV-positive patients, there may be an increase in visual field loss due to fatigue. To estimate the effects of fatigue on this study population, we compared the visual field indices of mean defect and CPSD with visual field severity grade between the first and second eyes tested in the 70 individuals, with both eyes available. There were no significant differences with order of testing for any of these measures. Also, no significant differences were noted when comparing the percentage abnormal of all eyes tested vs only the first eyes tested by severity group.

Results of the Kaplan–Meier survival analysis indicated a significant difference (P = .04) in time of survival between individuals with normal visual fields (28 [67%] of 42 of whom were still alive at time of analysis) and those with a visual field loss classified as abnormal due to a mean defect only (3 [33%] of 9 of whom remained alive) with a trend for decreasing survival with increase in visual field severity score (Figure 5).

COMMENT

In our previous work,13 we have also found a lack of correlation between CD4 cell count and global measures of visual field loss. It is apparent that vision loss can occur,
even when there is no obvious ocular pathologic lesion or diagnosis of AIDS. This stresses the need for early identification of abnormal vision, especially in light of our finding of a significant difference in time to survival for patients with relatively more advanced visual field loss compared with those with normal visual fields.

Because this is a cross-sectional study, we cannot be certain that field loss progresses from none to early to moderate to diffuse as HIV infection progressively attacks an individual. To be certain, we must continue to follow these same eyes over time. However, the trend toward decreased survival time in eyes with more advanced field defects, most notable and significant for those with diffuse loss throughout the visual field, suggests that visual field testing may provide an important predictor of advancing disease.

Other factors that may artifactually produce field defects should be taken into account. In this study, we controlled for several of them. Ptosis of the upper lid may cause a superior field defect similar to that seen in the early field loss group. Ptosis in individuals younger than 55 years is rare, but the visual field operator (D.J.P.) monitored the patients throughout testing to be sure that a droop of the eyelids did not cause the upper lid to approach the center of the pupil for less than a 2-mm clearance. Great care was taken to position the refractive

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**Table 1. Criteria for Determining Severity of Visual Field Loss Using the Glaucoma Hemifield Test (GHT), Corrected Pattern SD (CPSD), and Mean Defect (MD) Percentiles and Decibel Values**

<table>
<thead>
<tr>
<th>Severity</th>
<th>GHT, %</th>
<th>CPSD, %</th>
<th>MD, %</th>
<th>MD, dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;99.5 and &lt;95</td>
<td>&lt;95</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>&gt;99.5 or 95-99 with or without &lt;95</td>
<td>&lt;=-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;99.5 or &gt;99 with or without &gt;95</td>
<td>&gt;-6 but &lt;=-15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>&gt;99.5 or &gt;99 with or without &gt;95</td>
<td>&gt;-15 and &lt;=-25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD only</td>
<td>&lt;99.5 and &lt;95 with &gt;95</td>
<td>Any dB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 1. Topographic map of the nerve fiber layer showing 21 visual field zones used in the analysis of visual field data.**

**Figure 2. Percentage of eyes (151 eyes of 81 patients) with a defect in each of the 21 visual field zones broken into 4 categories of visual field defect. Each eye can have more than one defective zone. Fields were classified as human immunodeficiency virus (HIV) positive with normal visual fields (n = 88) (A), HIV positive with loss by mean defect only (n = 11) (B), HIV positive with early visual field loss (n = 32) (C), and HIV positive with moderate visual field loss (n = 20) (D).**
correction properly and to be sure the patient maintained proper alignment throughout testing.

Fatigue is another factor that can greatly influence test results. Patients showing any evidence of dementia on neuropsychologic testing were excluded from the study, as were those with unreliable visual fields (false-positives, false-negatives, and fixation losses exceeding 25%). A comparison between results of the first eye tested with the second eye tested showed no significant differences, suggesting that fatigue was not a major influence in these patients. Short-term fluctuations during the visual field test can also be an indicator of fatigue. However, increasing short-term fluctuation has been found to more often be an indicator of increasing vision loss.30 Finally, the pattern of deficit in the HIV-infected group was not consistent with that seen in patients with Alzheimer disease, in which the pattern reflects dementia, fatigue, or inattention. Patients with Alzheimer disease show deficits that are most pronounced in the inferior visual field, where they most commonly manifest as arcuate defects.31 In that study, simulations of inattention and fatigue produced diffuse defects with no particular pattern.31 Although we cannot completely rule out the influence of such other factors on the test results, it is unlikely that they would produce the consistent pattern of field loss that we found throughout all groups.

Permanent infarctions of the nerve fiber layer of the retina previously resolved or still evidenced by cotton-wool spots can, in the aggregate, produce visual field defects. Although it is possible that the defects found in the

### Table 2. Abnormal Visual Field Locations (Points) at Each of STATPAC’s Percentile Cutoffs for Each of the Visual Field Severity Categories

<table>
<thead>
<tr>
<th>Visual Field Category</th>
<th>STATPAC Cutoffs</th>
<th>Total Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.31 (1.44)</td>
<td>1.88</td>
</tr>
<tr>
<td>Early</td>
<td>3.47 (2.27)</td>
<td>7.54</td>
</tr>
<tr>
<td>Mean defect only</td>
<td>3.91 (2.95)</td>
<td>7.82</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.60 (2.98)</td>
<td>16.25</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD).
present study are the result of multiple infarctions, the resulting pattern would not be expected. For example, the nerve fiber layer infarctions that accumulate in diabetic retinopathy produce a generalized constriction and depression of the visual field not a pattern such as that seen in the present study. We also evaluated the fields for other typical patterns. There were no patterns of loss in the visual field to suggest chiasmal or postchiasmal hemianopia. In addition, defects that cross the horizontal midline (which would suggest outer retinal lesions rather than optic nerve or inner retinal lesions) were not seen except in 7 eyes, 5 of which were nasal step-like crossings at the 2 most peripheral nasal points tested. The other 2 had crossings at the most peripheral points temporal to the blind spot. The pattern seen in the HIV-positive individuals involved the superior and inferior regions of the visual field, consistent with damage at or near the optic nerve head. This pattern is an intriguing finding that requires histopathologic correlation with morphometric studies.

The effects of medications also could not be determined; however, none of these patients were taking suramin sodium, which is known to affect the optic nerve. Most patients (68/81) were taking zidovudine, which can affect the neural retina; to our knowledge, has not been studied in association with visual field loss. As mentioned previously, all patients in this study were evaluated before the introduction of highly active antiretroviral therapies.

The pattern of visual field loss found shows a relative sparing of the nasal step and arcuate bundle areas, where defects are more typically seen in glaucoma or early Alzheimer disease. The pattern is not diffuse as is often seen in diabetes. Neither a diffuse nor multiple focal retinal process is likely to result in the pattern of visual field loss shown herein, which appears uniquely different from the patterns reported for other disease states. The fact remains that this pattern is unique and consistently seen at all stages of field loss severity. This unique pattern, regardless of its physiologic basis, may be the most important finding of this study.

The identification of a pattern of early field loss in HIV-positive eyes, and the suggestion that severity of field loss may be a predictor of advancing disease, have implications for therapeutic follow-up of these patients. Patients with progressing field loss may require more aggressive therapies than those whose vision remains stable regardless of its physiologic basis, may be the most important finding of this study.

Accepted for publication December 15, 1998.

This study was supported by the University of California, San Francisco, grants AIDS R92-SD-135 and NEI EY08208 (Dr Sample), NEI EY07366 (Dr Freeman), AIDS R95-SD-082 and NEI EY11961 (Dr Plummer), and NEI EY09510 from The National Eye Institute, Bethesda, Md; RPB Senior Investigator Award 1997 (Dr Sadun); and grant MH45294 from the National Institute of Mental Health, HIV Neurobehavioral Research Center, Bethesda. Reprints: Pamela A. Sample, PhD, Department of Ophthalmology, University of California, San Diego, 9500 Gilman Dr, La Jolla, CA 92039-0946 (e-mail: psample@eyecenter.ucsd.edu).

REFERENCES