Confirmation of Visual Field Abnormalities in the Ocular Hypertension Treatment Study

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Objective: To determine the frequency with which visual field abnormalities observed on follow-up visual fields for patients in the Ocular Hypertension Treatment Study were confirmed on retest.

Methods: Between April 1, 1994, and March 1, 1999, 21,603 visual fields were obtained from 1,637 patients in the Ocular Hypertension Treatment Study. When follow-up visual fields are outside the normal limits on the Glaucoma Hemifield Test, the Corrected Pattern Standard Deviation (P<.05), or both, subsequent follow-up visual fields are monitored to confirm the abnormality. Abnormalities are confirmed if they are again abnormal on the Glaucoma Hemifield Test, the Corrected Pattern Standard Deviation, or both; if the defect is not artifactual; and if the same index and location are involved. Reliability criteria used by the study consisted of a limit of 33% for false positives, false negatives, and fixation losses.

Results: Of the 21,603 regular follow-up visual fields, 1,006 were follow-up retests performed because of an abnormality (n=748) or unreliability (n=258). We found that 703 (94%) of the 748 visual fields were abnormal and reliable, and 45 (6%) were abnormal and unreliable. On retesting, abnormalities were not confirmed for 604 (85.9%) of the 703 originally abnormal and reliable visual fields.

Conclusions: Most visual field abnormalities in patients in the Ocular Hypertension Treatment Study were not verified on retest. Confirmation of visual field abnormalities is essential for distinguishing reproducible visual field loss from long-term variability.


The Ocular Hypertension Treatment Study (OHTS) is a multicenter trial, funded by the National Eye Institute, National Institutes of Health, Bethesda, Md. The OHTS seeks to evaluate the safety and efficacy of topical ocular hypotensive medication in preventing or delaying the onset of visual field loss, optic nerve damage, or both in patients with ocular hypertension who are at moderate risk for developing primary open-angle glaucoma.1,2 Half of the patients receive topical ocular hypertensive medication, and half receive careful observation only. Automated static perimetry (Humphrey field analyzer program 30-2 full-threshold test; Humphrey Systems, Dublin, Calif) is used as one of the primary outcome measures for the OHTS.1 Progressive glaucomatous cupping, as determined from optic disc photographs, is also a primary outcome measurement for the OHTS.1,2 A detailed description of the OHTS protocol is available elsewhere.1,2

Automated static perimetry in patients with glaucomatous visual field loss exhibits large amounts of variability.3-11 For patients with ocular hypertension, the typical visual field has normal sensitivity, and variability has been reported to be lower than in glaucomatous visual fields.3-11 However, long-term longitudinal investigations12,13 of patients with ocular hypertension are limited. The present study examines the reproducibility of visual field abnormalities observed in patients with ocular hypertension who were enrolled in the OHTS. We determined the frequency with which visual field abnormalities observed on follow-up visual fields in the OHTS were confirmed on retest.

RESULTS

We report on 21,603 regular follow-up visual fields obtained between April 1, 1994, and March 11, 1999 (36 regular follow-up fields were not used because a Humphrey program 30-2 was not used), and 703 retests that were performed be-
MATERIALS AND METHODS

Before testing patients in the OHTS, technicians are required to complete a certification process that covers all aspects of OHTS’s visual field testing. Technicians must demonstrate that they can perform visual fields and enter patient data according to OHTS protocol. Informed consent was obtained from each patient before the study.

Visual field testing in the OHTS consists of automated static perimetry using program 30-2 on the Humphrey field analyzer. The visual field protocol used in the OHTS is a modification of the one used in the Optic Neuritis Treatment Trial. Testing includes a full-threshold test strategy, a 31.5-apostilb background, a size III target, a false-negative threshold determination, and a short-term fluctuation determination. The limit for fixation losses, false positives, and false negatives is 3% for the OHTS. If a patient’s pupils are less than 3 mm in diameter, the eyes are dilated before visual field testing. Dilation was noted in 562 (2.6%) of the cases. An appropriate lens correction is placed before the eye is tested, and the non-tested eye is occluded. If the lens correction exceeds 5 diopters, a soft contact lens correction is used to minimize trial lens rim artifacts.

All visual fields obtained for the OHTS are sent to the Visual Field Reading Center, University of California, Davis, for processing and analysis. Each field is evaluated by a comprehensive quality control system to determine if all aspects of the OHTS protocol were followed. The approach is similar to that used in the Optic Neuritis Treatment Trial. The quality control system addresses 3 areas of performance by the OHTS clinic technician and clinic coordinator, as shown in Table 1: (1) whether the correct visual field testing parameters were used (mean test parameter errors), (2) whether the patient data were entered correctly (patient data errors), and (3) whether visual field handling instructions were followed (shipment errors). Continuous feedback on the quality control findings is provided to the visual field technicians and the clinic coordinators. This feedback is provided in 3 primary ways: (1) individual reports are sent to the clinics for each visual field monthly, (2) summary reports regarding overall clinical performance are sent quarterly, and (3) telephone calls are made when necessary. The aim of this feedback is to ensure that visual field quality in the OHTS is optimal. In addition, the patients’ pupil sizes and refractions are monitored to minimize the possibility that they are causes of visual field abnormalities.

To enroll in the study, in addition to meeting other entrance criteria, patients needed 2 normal, reliable visual fields for each eye. A maximum of 3 visual field tests were allowed on each eye to obtain these 2 normal, reliable visual fields, and they had to be performed within a 3-month period. A technically acceptable visual field was considered to be normal if all visual field indexes were within normal limits and if there were no clusters of abnormal points that had low sensitivity and might be consistent with early glaucomatous damage. A cluster is defined as 2 or more horizontally or vertically contiguous abnormal points ($P < .05$), which could represent early stages of glaucomatous loss (eg, a subtle nasal step). A visual field was considered to be reliable if false positives, false negatives, and fixation losses were below 33%. Follow-up visual fields are obtained every 6 months. In the OHTS, the Glaucoma Hemifield Test and the Corrected Pattern Standard Deviation are the Humphrey indexes that are monitored to detect the development of possible glaucomatous visual field loss. Through 1997, if a technically acceptable follow-up visual field was abnormal on the Glaucoma Hemifield Test (outside normal limits or a general reduction of sensitivity), the Corrected Pattern Standard Deviation ($P < .05$), or both, a retest was performed on the eye in question within the same 6-month follow-up visit window, preferably within 8 weeks. A visual field abnormality was considered not confirmed if it was determined that it was artifactual (trial lens rim artifacts that disappear on retest or superior depression that disappears with taping of the eyelid) as judged by the Visual Field Reading Center readers. An abnormality was considered confirmed if the same index was involved on test and retest and if the abnormality was in the same general location (involving similar points as the previous visual field).

During follow-up, a high percentage of first abnormal visual fields were found to be normal according to OHTS standards on retest. Accordingly, a more stringent criterion for confirmation of visual field abnormalities was adopted effective January 1, 1998, at the recommendation of the OHTS Data and Safety Monitoring Committee, the OHTS Steering Committee, and the OHTS Full Investigative Group. The protocol was changed so that confirmation of a visual field abnormality required 3 consecutive visual fields with a defect of the same character in the same general location. Thus, a patient with an abnormal visual field is tested at the next regularly scheduled follow-up visit in 6 months. If the Visual Field Reading Center considers the second visual field abnormal, it requests a third visual field to be completed in 1 day to 8 weeks. If the visual field abnormality is confirmed on the third visual field, the Visual Field Reading Center prepares a narrative description of the abnormality and sends all visual fields to the OHTS Coordinating Center for review by the OHTS End Point Committee. The OHTS End Point Committee, which is masked as to randomization assignment, determines whether the visual field abnormality is clinically relevant and can be attributed to primary open-angle glaucoma based on a review of all clinical information. Unreliable follow-up visual fields (false-positive errors, false-negative errors, or fixation losses exceeding 33%) are also retested. However, if the visual field is again unreliable on retest, no action is taken, and the patient will simply be tested again at the next regularly scheduled visit. For this study, only abnormal and reliable visual fields were examined.
Figure 1 shows the overall quality control performance of the OHTS clinical centers for a quarterly grading system during a 2-year period (January 1, 1997, to December 31, 1998). Each visual field is graded on a 100-point scale, as described in Table 1. On this scale, 0 represents a perfect score and 100 represents the maximum number of error points (Table 1). Fifty-nine percent (12,831/21,603) of the follow-up visual fields had perfect scores of 0 errors. As shown in Figure 1, the overall visual field performance at the OHTS clinical centers has been excellent, with a quarterly mean consistently around 2 error points per visual field and the mean number of error points declining over time.

Table 2 shows the results for the retest visual fields that directly followed the 703 technically acceptable abnormal visual fields. Some of the abnormal visual fields were from the same eye at different follow-up visits. The initial abnormality was confirmed on 99 (14.1%) and not confirmed on 604 (85.9%) of the 703 originally abnormal visual fields. The 604 abnormalities that were not confirmed fell into 3 categories: (1) 467 (66.4%) tested within normal limits on all indexes; (2) 112 (15.9%) were normal according to OHTS standards but had a borderline result on at least one index; and (3) 25 (3.6%) were abnormal according to OHTS standards, but the defect was due to artifact, in a different location, or on a different index than on the preceding visual field. A review of refractive error and pupil size information revealed that they could not have been a contributory factor in any of the nonconfirmed visual field abnormalities. A few nonconfirmed visual field losses could be attributed to a heavy eyebrow or droopy eyelid (6 [0.9%] of 703) or to trial lens rim artifacts (3 [0.4%] of 703).

In most cases, nonconfirmation of visual field abnormalities in patients in the OHTS does not appear to be related to uncooperative patients, protocol violations, or careless test administration. Unreliable visual fields were not included in the data analysis for this study. However, only 389 (1.8%) of the 21,603 regular follow-up visual fields exceeded the 33% limits for fixation losses, false-positive errors, or false-negative errors. As shown in Figure 1, the excellent quality control scores attest to the outstanding performance of visual field technicians and clinic coordinators in the OHTS (0.17% [36/21,603] of the follow-up visual fields were unusable due to a non–30-2 test strategy). In addition, the low rate of unreliable visual fields is related to our enrollment criteria requiring 2 reliable fields.

Of the 9 cases of artifactual results, 2 are shown in Figure 2 and Figure 3. These artifacts accounted for a small portion of abnormal test results and were not confirmed on retest. Figure 2 provides an example of a probable trial lens rim artifact that disappears on retest. A high plus lens correction was used, increasing the likelihood that this was a trial lens rim artifact. Figure 3 provides an example of a probable droopy upper eyelid producing a superior visual field loss that is not present on retest. As shown in Figures 4, 5, 6, and 7, most cases included visual field loss that was typical of localized glaucomatous defects. Figure 8 provides an atypical example of visual field loss (cause unclear) that resolves on retest.
COMMENT

Previous investigations\textsuperscript{3,11,15-44} have reported that automated static perimetric threshold tests exhibit variability, within a test procedure and from one examination to another. In normal subjects, this variability is between 2 and 3 dB.\textsuperscript{15-17} Several factors have been shown to affect the amount of variability in normal subjects, including target size,\textsuperscript{18,19} visual field eccentricity,\textsuperscript{15-17} age,\textsuperscript{16,17,20} and threshold sensitivity.\textsuperscript{20}

In patients with glaucomatous visual field loss, the amount of variability is much higher,\textsuperscript{3-10} with greater variability for locations with reduced sensitivity.\textsuperscript{20}

Heijl and colleagues\textsuperscript{4,21} found that the 95% confidence interval for the variability in normal subjects is between 2 and 3 dB.\textsuperscript{15-17}

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In patients with glaucomatous visual field loss, the amount of variability is much higher,\textsuperscript{3-10} with greater variability for locations with reduced sensitivity. The variability of threshold determinations for moderate visual field loss can be 3 to 4 times as large as for regions with normal sensitivity. Heijl and colleagues\textsuperscript{4,21} found that the 95% confi-
Dience limits for moderate visual field loss (8-18 dB of loss) encompassed nearly the entire measurement range (0-40 dB) of the Humphrey field analyzer. In patients with ocular hypertension, the visual field has normal sensitivity, and variability is much lower than in those with glaucoma. Werner et al. have reported that the variability of visual fields in patients with ocular hypertension is only slightly higher than in normal subjects. Thus, one might expect glaucomatous visual field changes in patients with ocular hypertension to be more reliable than moderate glaucomatous visual field defects.

Variability in visual fields, which may be due to factors unrelated to optic nerve pathological features, is not limited to glaucoma. Similar results of high variability in areas of visual field loss have been reported for optic neu-
rinitis.22 Wall et al22 examined the short- and long-term variability of automated perimetry in healthy subjects and in patients with optic neuritis who were thought to be stable and who had a residual visual field (Humphrey mean deviation of −3.00 to −20.00 dB). Patients with optic neuritis demonstrated variations in visual field sensitivity that were outside the entire range of the variability for normal controls. In the present study, the cause of the abnormality (whether it be early glaucomatous or not) can only be defined when the OHTS is completed.

The 85.9% rate of visual field abnormality not being confirmed after a single abnormal visual field in this study indicates that there is considerable variability in the visual fields of patients with ocular hypertension as they begin to show early glaucomatous visual field loss. Previous studies have reported that increased visual field variability may be an early sign of glaucomatous damage. Hart and Becker23 believe that glaucomatous visual fields go through 3 phases: the first is the initial stage, with no defect demonstrable despite the fact that occult damage is occurring. The second is a period in which shallow defects are often transient and are rarely detectable. The chronological course of initial visual field defects was marked in 22 of the 98 eyes by a phenomenon of transiently appearing defects. In the third phase, visual field defects progress at an uneven pace to become dense. The transient nature of initial visual field defects (at the threshold stage) and the invariant findings of their greater density on recurrence was considered by Hart and Becker to be the best evidence of progressive damage occurring to the visual system before its detection by light-sense perimetry. The OHTS should help us to understand whether abnormal visual fields that return to normal are the first stage of progressive glaucomatous field loss or are simply long-term variability. In addition, the OHTS should also help to determine the significance of a single abnormal test result. The OHTS will be able to determine if patients with abnormal or borderline visual fields that return to normal have a different long-term prognosis than patients who do not have any abnormal visual fields.

In patients with progressive glaucoma, there are difficulties in distinguishing between truly progressive glaucoma and long-term variability unless several visual fields are obtained over time. Werner24 concluded that a minimum of 6 visual fields were needed to make informed clinical judgments as to whether a patient’s visual field was stable or progressing. Quantitative approaches using linear regression have come to similar conclusions, indicating that approximately 7 visual fields obtained over several years are needed to reliably distinguish progression from intratest variability.25-28

For studies using a discrete measure (change from baseline) rather than regression techniques, it has been found that confirmation of changes are necessary to avoid “overcalling” progression of visual field loss. In the Normal-Tension Glaucoma Study, Schulzer29 found that 4 to 6 confirming visual field tests (2 of 3 tests performed within 1 to 4 weeks showing change, followed by 2 of 3 tests performed 3 months later) were needed to reliably determine visual field progression. Chauhan and colleagues30 defined progression as at least 4 nonedge test locations that were beyond the 5% probability level on the Glaucoma Change Probability program (significant change from baseline) and a confirming field with complete overlap of at least 4 of these locations. The Early Manifest Glaucoma Trial31 uses a similar strategy, except the Glaucoma Change Probability is based on the pattern deviation values rather than on the total deviation values and 3 locations beyond the 5% level need to be confirmed on 3 successive tests.

Several strategies have been attempted to reduce the variability associated with conventional automated perimetry.32-39 Because of the strict OHTS quality control system that provides regular feedback to the clinical centers and the visual field technicians about their performance and handling of the visual fields, visual field quality has not been a factor in the variability. Only 1.8% of the 21,603 regular follow-up visual fields (fixation losses, false-positive errors, or false-negative errors) were beyond the 33% limit. In addition, neither pupil size nor refractive errors contributed to the variability. Unreliable visual fields were not included in the present study. We will have a better understanding of whether these abnormalities are due to early transient pathological features, unreliable fields, or a combination of both with further follow-up evaluations. Because of the variability demonstrated in the present study, the OHTS has changed its visual field protocol for confirming abnormality. Three consecutive abnormal visual fields are required, for which the defect is not artifactual, the same index is involved, and the abnormality is in the same location.

Our results indicate that most of the initial visual field abnormalities in the patients in the OHTS are not reproduced on retest. Confirmation of visual field abnormalities through retesting is essential for distinguishing the development or progression of glaucomatous visual field loss from long-term variability.

![Figure 8. This example shows consecutive follow-up fields for the left eye of a patient in the Ocular Hypertension Treatment Study. Top, The first test, performed on July 30, 1997, shows an inferior temporal vertical step (cause unclear). The prescription used was a −3.50-diopter sphere. The pupil diameter was 6.0 mm. The results of the GHT were outside normal limits, and the CPSD was P < .05. Bottom, The inferior temporal vertical step resolved on the retest, performed on September 15, 1997. The prescription used was a −3.50-diopter sphere. The pupil diameter was 5.0 mm. The results of the GHT and the CPSD were normal.](Image 70x653 to 290x742)
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Ocular Hypertension Treatment Study (OHTS) Group (cont)