Prediction of Glaucomatous Visual Field Loss by Extrapolation of Linear Trends

Boel Bengtsson, PhD; Vincent Michael Patella, OD; Anders Heijl, MD, PhD

Objective: To investigate how well short-term progression rates can predict long-term visual field outcomes in patients with glaucoma.

Methods: We calculated visual field rates of progression using linear regression analysis of the Visual Field Index (VFI) for 100 consecutive patients with glaucoma having 10 or more Swedish Interactive Thresholding Algorithm standard field tests. Final VFI was predicted on the basis of linear extrapolation of the slope defined by the initial 5 field test results. Final VFI also was estimated using linear regression of all qualifying examination results for each patient. Primary outcome measures were the absolute difference and the correlation between predicted and estimated final VFI values.

Results: Patient follow-up averaged 8.2 years and 11 field examinations. Median VFI progression rate was −1.1% per year both for the initial 5 test results and also for the complete series. Seventy percent of patients had a predicted final VFI within ±10% of the estimated final VFI, and the 2 VFI calculations had a correlation coefficient of 0.84.

Conclusion: Linear extrapolation based on 5 initial visual field test results was a reliable predictor of future field loss in most patients. Patients in whom linear regression analysis suggests dangerously rapid rates of visual field progression may be candidates for significant alterations in therapy.

Arch Ophthalmol. 2009;127(12):1610-1615

Visual field testing occupies a central role in the management of patients with glaucoma. Standard automated perimetry provides quantitative measurements suitable for automated statistical analysis of visual field change over time. Methods for identification of progressive visual field loss have been developed,1-4 as well as criteria for defining outcomes in clinical trials.5-8 These event-based methods were primarily designed to indicate whether statistically significant progression has occurred. Event-based methods also are used in clinical practice as aids in differentiating between random measurement noise vs true change and may be particularly useful for identifying statistically significant change in patients with newly diagnosed glaucoma. In the long-term, however, most patients with glaucoma may be expected to show some degree of progression, since glaucoma is a progressive disease. As an example, after an average of 8 years of follow-up in the Early Manifest Glaucoma Trial, 59% of treated patients had shown progression vs 76% in the control arm.9

Event-based analyses provide little information about rate of change. Pointwise or cluster-based trend analyses provide the focal or regional rate of change, helping to detect whether progression has occurred. Trend analysis using a global index is not particularly sensitive to early detection of progression but provides information about the global rate of change. Therefore, global trend analysis showing patients’ rates of progression may be particularly useful in the long term. We have seen both in clinical trials10,11 and in clinical practice12 that the yearly global rate of progression varies widely among patients with glaucoma. Knowledge about the rate of progression can help to identify those patients who are progressing so rapidly that they are at serious risk for developing visual disability. These patients can then receive more aggressive treatment and/or more frequent follow-up as compared with patients showing no progression or only slow rates of progression.
Rate of progression estimates displaying the yearly rate of change in decibels of mean deviation or mean defect, or other global indexes, have been available for more than 20 years. These analyses, displaying linear trends in graphs, can assist clinicians in individualizing management of patients with glaucoma. Mean deviation or mean defect indexes, however, are affected by cataract and can therefore give erroneously high rates of progression in patients with glaucoma with increasing cataract, or true glaucoma progression can be masked by cataract surgery.

We have previously reported the development of a new summary Visual Field Index (VFI) designed to be relatively resistant to cataract. The VFI expresses visual function as a percentage of a perimetrically normal age-corrected visual field and is used for calculation of rate of progression by regressing VFI over time as expressed by patient age.

Linear estimates of rate of progression have been found to be better predictors of glaucomatous progression than intraocular pressure and other risk factors and to predict future field loss more accurately than other more complex nonlinear models. We wished to investigate how well short-term linear estimates of progression rates predict long-term outcomes. The goal of the present study was to investigate and quantify how well extrapolation of linear estimates of visual field loss can predict future field loss in patients with glaucoma being managed in ordinary glaucoma practice.

METHODS

PATIENTS

Consecutive patient records having 10 or more automated threshold visual field tests were retrospectively selected from a database consisting of all patients with glaucoma managed for 5 or more years at the Department of Ophthalmology, Malmo University Hospital, Malmo, Sweden. All candidate patients had a clinical diagnosis of glaucoma in at least 1 eye. Diagnosis was based on typical glaucomatous optic disc changes, eg, neuroretinal rim notching or narrowing, with corresponding visual field defects. Some patients were initially followed up for suspect glaucoma in the absence of field defects and developed glaucomatous field defects during the course of follow-up. Patients having concomitant diseases known to affect the visual field, other than cataract, were excluded. No restrictions on visual acuity, amount of visual field loss, or type of treatment were applied. The regional board for vetting ethics of research involving humans in Lund, Sweden, approved the study.

One eye per patient was included in the analysis. In patients with unilateral glaucoma, the affected eye was selected; in patients with bilateral glaucoma, 1 eye was randomly selected for analysis.

VISUAL FIELD TESTS

Humphrey Swedish Interactive Thresholding Algorithm (SITA) standard 30-2 or 24-2 examinations are the standard visual field test used for management of patients with glaucoma at the Department of Ophthalmology in Malmo. Thus, all visual field test series consisted only of SITA standard tests. All visual field test results of all enrolled patients were included, except that test results having 15% or more false-positive response rates were considered unreliable and thus were excluded. The 15% limit was based on the 95th percentile of the empirical distribution of false-positive answers among healthy subjects collected for calculation of the SITA Statpac. False-negative answers cannot be well estimated in eyes having visual field defects and were therefore ignored. The VFI was the index used for calculation of rate of progression.

The calculation of VFI has earlier been described in detail, but briefly, VFI is a summary index calculated from the 52 test points included in the 24-2 test point pattern. Test points with normal function (≥95% in the pattern deviation probability maps) are scored to have 100% sensitivity. Test points having absolute defects, defined as measured threshold sensitivities less than 0 dB, are scored to have 0% sensitivity. The sensitivity at points with reduced function (<5% in the pattern deviation probability maps), but not blindness, is scored using the defect depth and age-corrected normal threshold value. The VFI is an eccentricity-weighted mean of the scores at all 52 test points.

ANALYSES

Rates of progression were calculated by linear regression analysis of the VFI over time. The VFI is less sensitive to cataract than older global indexes used for calculation of rate of progression and is expressed in percentage, where 100% represents a normal visual field and 0%, a perimetrically blind field. Thus, the rate of change is presented as the yearly change in percentage per year.

Linear regression analysis of VFI values for the first 5 field tests for each patient was used to calculate the initial rate of progression (Figure 1A). A second rate of progression was calculated on the basis of linear regression analysis of each patient’s full series of visual field tests (Figure 1B). The difference between the initial and full series rates of progression was calculated for each subject and presented in terms of median and range.

We also used these 2 rates of progression to calculate VFI values (labeled “predicted” and “estimated”) on the date of the last field test in the full series. Predicted and estimated values lower than 0% and higher than 100% were set to −1% and 101%, respectively. The range of VFI was truncated since VFI can never be lower than 0% or exceed 100% in real tests. Predicted VFI was compared with the estimated VFI in a scatterplot, and a linear regression analysis was performed. The procedure was repeated after excluding 13 patients starting with at least 2 normal visual field test results, defined by a glaucoma hemifield test result “within normal limits.” To eliminate possible clumping effects caused by the truncation on the correlation between the estimated and predicted VFI, a third regression analysis was performed excluding those (n = 13) having truncated VFI values.

The influence of baseline visual field status, as described by VFI, on the rate of progression and the ability to predict the final VFI was tested by linear regression analysis. The effect of the duration of both the total and the initial (ie, the first 5 tests) periods on the ability to predict VFI was analyzed by linear regression.

RESULTS

Among the first 100 patient medical records having 10 or more field tests, 1 record contained a number of unreliable test results (more than 15% false-positive answers). After exclusion of these test results, the record’s full series no longer included the 10-test limit required for inclusion in the analysis, so 1 additional patient rec-
ord was retrieved to raise the total back to 100 patients. No patients, except the 1 excluded, had any unreliable field test results. Mean patient age at the start of the series was 72 years, ranging from 49 to 89 years. Forty-one percent had undergone cataract surgery during follow-up. Approximately 20 different physicians had managed the 100 patients. Descriptive statistics on number of tests and follow-up time and visual field status at the start of the series are displayed in the Table.

The median rate of progression of VFI for the first 5 field tests was –1.5% per year, which was the same as the median rate for the full series. The median absolute difference between the initial and full series rates of progression was 1.1% per year, ranging from 0% to 13.8%.

The predicted VFI, calculated by linear extrapolation of the trend of the first 5 field test results to the date of the last field test in each series, correlated well with the estimated VFI based on the full series ($r = 0.84$) (Figure 3A). When excluding 13 subjects who all started with at least 2 normal visual field test results, the correlation coefficient increased to 0.88 (Figure 3B). The correlation coefficient was 0.78 when comparing the predicted VFI with the actual last VFI including all subjects, and the correlation coefficient was 0.79 after repeating the first analysis again but this time ignoring those with VFIs truncated to −1% or 101%.

In 45% of subjects, the final VFI predicted on the basis of the initial 5 field tests differed by less than ±5% from the final VFI estimated using the full series; 70% differed by less than ±10% from the estimated VFI; and 3% of the subjects differed by 50% or more.

The median rate of progression of VFI for the first 5 field tests was –1.5% per year, which was the same as the median rate for the full series (Figure 2). The median absolute difference between the initial and full series rates of progression was 1.1% per year, ranging from 0% to 13.8%.

The predicted VFI, calculated by linear extrapolation of the trend of the first 5 field test results to the date of the last field test in each series, correlated well with the estimated VFI based on the full series ($r = 0.84$) (Figure 3A). When excluding 13 subjects who all started with at least 2 normal visual field test results, the correlation coefficient increased to 0.88 (Figure 3B). The correlation coefficient was 0.78 when comparing the predicted VFI with the actual last VFI including all subjects, and the correlation coefficient was 0.79 after repeating the first analysis again but this time ignoring those with VFIs truncated to −1% or 101%.

In 45% of subjects, the final VFI predicted on the basis of the initial 5 field tests differed by less than ±5% from the final VFI estimated using the full series; 70% differed by less than ±10% from the estimated VFI; and 3% of the subjects differed by 50% or more.

Rate of progression was independent of the baseline VFI ($P = .39; r^2 = 0.06$) when excluding 4 eyes starting with seriously damaged fields with VFI of 20% or less. These 4 eyes had a smaller rate of change than those starting at

### Table. Descriptive Statistics of the Patients With Glaucoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total follow-up time, y, mean (range)</td>
<td>8.2 (5.4 to 9.9)</td>
</tr>
<tr>
<td>Follow-up time for first 5 field tests, y,</td>
<td>3.3 (1.3 to 7.7)</td>
</tr>
<tr>
<td>mean (range)</td>
<td></td>
</tr>
<tr>
<td>No. of visual field tests in complete series</td>
<td>11 (10 to 16)</td>
</tr>
<tr>
<td>VFI first visual field test, %</td>
<td>88.7 (91.1 to 99.9)</td>
</tr>
<tr>
<td>MD first visual field test, dB</td>
<td>−5.75 (−28.82 to +1.53)</td>
</tr>
</tbody>
</table>

Abbreviations: MD, mean deviation or mean defect; VFI, Visual Field Index.
better levels, an effect most likely explained by truncation. The median rate of progression was 0.6% per year among these eyes and 1.5% per year among the other 96 eyes. The ability to predict the final VFI was not affected by baseline VFI ($P=.35; r^2=0.009$).

The difference between the predicted and estimated values was not affected by the total duration of the series (linear regression, $P=.59; R^2=0.003$), but it was by the duration of the initial period when the first 5 tests were assessed. The duration for this initial period averaged 3.3 years. The error of the prediction decreased 2.4% per year, suggesting the benefit of a longer initial period ($P=.10$).

**COMMENT**

We have evaluated the use of observed glaucomatous visual field progression rates in predicting future visual field loss. Our results suggest that in the majority of patients with glaucoma, future visual field loss can be predicted with some accuracy by linear extrapolation based on the VFI values of the first 5 visual field tests. This seemed to be particularly true when starting the analysis from a baseline where field defects already were present. Series starting with normal field test results might be expected to be less linear than those starting with test results containing significant visual field defects.

Among our patients, the duration for the initial period averaged 3.3 years. Longer initial periods might be expected to result in more accurate predictions of future field loss; our data suggest that a longer duration for the first 5 field tests decreases the prediction error. On the other hand, keeping the initial period as short as possible may enable earlier identification and earlier treatment adjustments in patients with rapidly progressing disease.

We are not suggesting that observed past rates of visual field loss must continue into the future. Quite the contrary, we propose that early determination of the progression rate may help identify patients with dangerously progressing disease who may well require a change in therapy. The clear goal of such therapeutic changes would be to significantly reduce the rate of progression to a more acceptable level. Likewise, observations of no or very slow progression may suggest that current therapeutic strategies have been successful. We realize that early identification of patients with rapidly progressing disease may require extra testing in the first few years after diagnosis. It remains to be seen what patient benefits result from such additional efforts.

Subjects included in this study were ordinary patients who were being managed in a hospital-based primary glaucoma care clinic; about 40% underwent cataract surgery during follow-up. The number of physicians examining these patients was quite large (about 20); thus, our results were not based on the practice patterns of just a few clinicians.

We believe that our patients were representative patients with clinical glaucoma for this part of the world. One can of course argue that patients with long series of field tests are more likely to be those with a fast progression rate, but this seemed not to be the case among our patients. The mean rate of visual field testing was 1.5 examinations per year, and no eye had more than 2 tests per year. Further, patients with faster rates of progression (steeper negative slopes) were not tested more often than those with slow progression. A regression analysis of slope vs number of tests showed no association at all; the regression coefficient was 0.07 slope/test ($P=.71$). Seventy-four of the 100 included patients started with or converted from the full-threshold program to SITA already in 1996 or 1997, which explains why we had a number of patients with long series of SITA field tests.
While it was not our intention to study treatment effect on rate of progression, one might reasonably wonder why progression rates in a university-managed cohort of patients were not being driven noticeably lower over time by the application of increasingly aggressive therapies. One possible answer is that patients might have been largely managed on the basis of individual intraocular pressure response to therapy and not on the basis of observed changes in ocular function or structure. Another alternative is that progression rates actually were slowed because of intensification of therapy over time. Results from clinical trials suggest that the course of glaucomatous disease may accelerate over time, while our results showed a small decrease in rate of change after the first 5 field tests. However, these questions cannot be answered by the present study.

The current rate of progression calculations assume that glaucomatous visual field damage occurs at a more or less constant rate, and this question of linearity has been previously evaluated. Long-term studies have reported that a linear fit of observed data provides the best model in a majority of patients and also that a linear analysis best predicts future progression. Others have reported nonlinear or episodic progression to be just as common. Smith and coworkers and Katz and coworkers described progression as episodic over relatively short periods but found a linear model to be more suitable in the long-term, where underlying episodic changes appeared as background noise. Our results, as well, suggest a linear course of progression in the long-term and also that the linear fit of the first 5 tests often can predict future field loss with considerable accuracy using the global VFI. The result should also apply to rate of progression calculated with the mean deviation index; the correlation between VFI and mean deviation recalculated into percentage was 0.97. In a previous article, we compared the rate of progression with the mean deviation or mean defect, recalculated into percentage, and VFI. The progression rates were very similar in pseudophakic eyes.

It would be ideal to restart rate of progression calculations whenever there is a significant change in therapy, thus improving the ability to identify important break points in the progression line. Currently available commercial software allows physician designation of new baseline field tests whenever such therapeutic changes occur. However, this requires more testing than is currently common and each clinic must consider when such re-baselining is deemed necessary.

In conclusion, linear regression estimates of rate of progression using 5 visual field test results obtained over a few years appear to predict future progression often enough to be useful as one element of a comprehensive evaluation of the adequacy of current therapy. Patients in whom linear regression analysis suggests dangerously rapid rates of visual field progression may be candidates for significant alterations in therapy.

Submitted for Publication: December 17, 2008; final revision received April 9, 2009; accepted June 19, 2009.

Correspondence: Boel Bengtsson, PhD, Departments of Clinical Sciences and Ophthalmology, Lund University, Malmo University Hospital, SE–20502 Malmo, Sweden (boel.bengtsson@med.lu.se).

Financial Disclosure: Drs Bengtsson and Heijl are both consultants of Carl Zeiss Meditec and receive research funding from Carl Zeiss Meditec. Dr Patella is an employee of Carl Zeiss Meditec.

Funding/Support: This study was supported by an unrestricted grant from Alcon Research Ltd, Forth Worth, Texas, Swedish Research Council grant K2005-74X-10426-13A, the Herman Jarnharl Foundation, the Foundation for Visually Impaired in Former Malmöhus lan, and Crown Princess Margaretta’s Foundation for the Visually Impaired.

REFERENCES


**Correction**

Errors in Figure and Text. In the Clinical Sciences article titled “Inner Retinal Layer Thinning in Parkinson Disease” by Hajee et al, published in the June issue of the Archives (2009;127[6]:737-741), errors occurred in the legend to Figure 3 and the text. The legend should have read, “Correlation between the mean inner retinal layer (IRL) and outer retinal layer (ORL) thickness in early Parkinson disease (r=0.31).” Also, in the “Results” section of the text on page 739, the paragraph entitled “Intercorrelation of IRL Thickness in Early PD” should have immediately preceded Figure 3 and its legend and should have read, in its entirety, as follows: “Figure 3 illustrates a correlation between the left and right eyes of patients with relatively early PD. The corresponding statistics revealed a correlation coefficient of 0.82.” The paragraph entitled “Correlation Between Mean IRL and ORL in Early PD” should have read as follows: “In Figure 4, an insignificant correlation was found between IRL and ORL thickness in the eyes of patients with relatively early PD. The corresponding statistics revealed a correlation coefficient of 0.31.”