Course of Glaucomatous Visual Field Loss Across the Entire Perimetric Range

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IMPORTANCE

Identifying the course of glaucomatous visual field (VF) loss that progresses from normal to perimetric blindness is important for treatment and prognostication.

OBJECTIVE

To model the process of glaucomatous VF decay over the entire perimetric range from normal to perimetric blindness.

DESIGN, SETTING, AND PARTICIPANTS

A post hoc, retrospective analysis was performed using data from the Advanced Glaucoma Intervention Study and the UCLA (University of California, Los Angeles) Jules Stein Eye Institute Glaucoma Division. Patients with open-angle glaucoma and VFs obtained from reliable examinations (defined as <30% fixation losses, <30% false-positive rates, and <30% false-negative rates) were recruited. All tests were performed with standard automated perimetry and a 24-2 test pattern. Linear, exponential, and sigmoid regression models were used to assess the pattern of threshold sensitivity deterioration at each VF location as a function of time. Visual field locations of interest included those with a mean of the initial 2 sensitivities of 26 dB or greater and a less than 10-dB mean of the final 2 sensitivities. Root mean squared error (RMSE) was used to evaluate goodness of fit for each regression model. The error was defined as the difference between the sensitivities modeled by the function and the observed sensitivities. The Advanced Glaucoma Intervention Study was conducted from 1998 to 2006; the present post hoc analysis was conducted from March 1, 2014, to March 1, 2015.

MAIN OUTCOMES AND MEASURES

The RMSE of the residuals (fitted minus observed values) for the 3 regression models was used to evaluate goodness of fit.

RESULTS

A total of 798 eyes from 583 patients (mean [SD] age, 64.7 [10.7] years; 301 [51.6%] women) who had more than 6 years of follow-up and underwent more than 10 VF examinations were included in this analysis. Mean (SD) follow-up time was 8.7 (2.2) years, and each eye had a mean of 15.2 (4.9) VF tests. For the VF locations with an initial sensitivity of 26 dB or greater and final sensitivity of less than 10 dB (309 locations), the sigmoid best-fit regression model had the lowest RMSE in 248 (80.3%) of the locations, the exponential function in 39 (12.6%), and the linear function in 22 (7.1%). The means (SDs) of RMSE were sigmoid, 4.1 (1.9); exponential, 6.0 (1.5); and linear 5.8 (1.6).

CONCLUSIONS AND RELEVANCE

Pointwise sigmoid regression had a better ability to fit perimetric decay into a subset of locations that traverse the entire range of perimetric measurements from near normal to near perimetric blindness compared with linear and exponential functions. These results support the concept that the measured behavior of glaucomatous VF loss to perimetric blindness is nonlinear and that its course of deterioration may change with the course of disease.
Glaucoma, a progressive optic neuropathy characterized by typical structural changes of the optic nerve head and retinal nerve fiber layer as well as deterioration of visual function, is a leading cause of blindness worldwide. Longitudinal visual field (VF) testing, as measured by standard automated perimetry, has become a standard for the evaluation of functional deterioration in glaucoma. Static perimetry quantitative measurements have been used to model disease progression. Linear models of disease are prevalent, but they assume that the rate of progression is constant over the entire range of perimetric sensitivities. Nonlinear models, such as the pointwise exponential model, have been shown to fit the progression of deterioration and to model the future better than linear models. As such, it would not be unreasonable to speculate that, during specific circumstances in the disease course, the VF deteriorates logarithmically. However, neither the exponential nor the linear model can account for phases of the disease during which the deterioration is not logarithmic or linear. Neither linear nor exponential models are likely to take into account the pattern of progression over the entire glaucomatous process or track the behavior of a single test location from normal to perimetric blindness.

We hypothesized that VF deterioration in glaucoma cannot be explained with models that require constant change over time and that the deterioration of perimetric sensitivity from normal to perimetric blindness may be better represented by a model that accounts for periods of time during which there is slow or no change, followed by a more rapid intermediate phase and a final period of stabilization (when the rate of measurable change is near levels of perimetric blindness). A model with these phases would resemble an inverted sigmoid function with natural asymptotes at normal perimetric sensitivity and at perimetric blindness (0 dB) and may better represent the course of visual dysfunction from normal to severely affected. To test this hypothesis, we proposed using a nonlinear sigmoid function as a model to represent the process of glaucomatous damage over the entire perimetric dynamic range and compared it with linear and exponential regression models.

### Methods

**Patient and VF Data**

Patient data from the Advanced Glaucoma Intervention Study (AGIS), which was conducted from 1998 and 2006, and the clinical database at the Jules Stein Eye Institute's Glaucoma Division were our combined study sample. Patients with reasonably reliable VFs, defined as having less than 30% fixation losses, less than 30% false-positive rates, and less than 30% false-negative rates, were recruited for the study. A total of 798 eyes from 583 patients who had more than 6 years of follow-up and underwent more than 10 VF examinations were included. The tests were performed with a Humphrey Field Analyzer (Carl Zeiss Ophthalmic Systems Inc) with the 24-2 test pattern, size III white stimulus, and full-threshold strategy or Swedish interactive threshold algorithm (SITA) standard or SITA fast strategies. Each eye's VF series contained either all SITA or all full-threshold examinations; examinations were never mixed for any eye in the series. This post hoc analysis study was approved by the UCLA (University of California, Los Angeles) Human Research Protection Program, with the need for informed consent waived, and by the individual institutional review boards of the clinical centers involved in the AGIS. The study was performed in accordance with the tenets set forth in the Declaration of Helsinki and complied with Health Insurance Portability and Accountability Act regulations. The methods for obtaining VF data have been described in detail elsewhere. The present study was conducted from March 1, 2014, to March 1, 2015.

The 24-2 program of the Humphrey Field Analyzer records threshold sensitivities (in decibels) of 54 locations, including the physiologic blind spot. Once the 2 test locations corresponding to the physiologic blind spot and locations with the initial 3 values equal to 0 dB were excluded, 3 regression models were used to assess the course of threshold sensitivity deterioration at each test location during the follow-up period for each eye.

**Regression Modeling**

The association between the response variable (y, threshold sensitivity) and the explanatory variable (x, duration of follow-up) was characterized by 3 regression models. These models included linear, first-order exponential, and a sigmoid function.

**Linear Regression Model**

In the linear regression model, expressed as \( y = a + \beta x \), a straight line indicates the association between the dependent variable y and the independent variable x, with a representing the intercept (an estimate of initial sensitivity measured in decibels), and \( \beta \) being the regression coefficient (slope) (an estimate of linear change in sensitivity per year measured in decibels per year). The ordinary least-squares method is used to estimate the regression of y on x. The linear model was censored at 0 dB. The value 0 dB was used if the fit produced a negative decibel value.

**First-Order Exponential Regression Model**

The first-order regression model is expressed as \( y = e^{\alpha + \beta x} \), or equivalently, \( \ln y = a + \beta x \), with a representing the slope of ln (natural log) y, where \( e^\alpha \) is an estimate of the annual rate of change (increase or decrease) in sensitivity (in rate per year);
Sigmoid Regression Model Analysis

We used mathematical equations (eAppendix in the Supplement) to measure the drop-off, level-off, and inflection points as well as the rate of decay at these points for the subset of test locations that had an initial mean sensitivity value greater than 22, 26, and 30 dB, all with a final mean sensitivity of less than 10 dB.

Results

Patient and VF Data

A total of 798 eyes from 583 patients were included in this study. The mean (SD) follow-up time was 8.7 (2.2) years, the total number of data series (with a mean of 50.6 [5.7] locations for each of 798 eyes) was 40,398, and the mean number of VF tests was 15.2 (4.9) for each VF location. The VF test strategies included SITA standard (6238 [43.7%]) and SITA full threshold (8036 [56.3%]). The characteristics and demographic data for the study group are reported in Table 1. Frequency distributions of the initial and final VF sensitivities for all locations are shown in Figure 1.

Postregression Diagnostics

For all 40,398 test locations, the mean (SD) RMSE values for each model were 3.0 (1.7) dB for the sigmoid regression model, 3.1 (1.8) dB for the exponential regression model, and 3.1 (1.8) dB for the linear regression model. For each location, the model with the lowest RMSE value was considered as the best fit for the location, and the percentages of best fits for each model were 52.8% (21,339 locations) for the sigmoid regression model, 42.7% (17,263 locations) for the exponential regression model, and 4.4% (1,796 locations) for the linear regression model (Table 2).

There were a total of 36 locations with an initial mean sensitivity value greater than 30 dB and a final mean sensitivity value less than 10 dB; each of the 3 model fits for these locations is shown in the eFigure in the Supplement; 8 sample locations are shown in Figure 2. The summary of model fits for these 36 locations can be found in Table 2.

Table 1 presents the mean RMSE values for the subsets of locations that had an initial sensitivity greater than 22, 26, and 30 dB, all with a final sensitivity of less than 10 dB. The mean (SDs) RMSE for the subsets for each model (initial mean, 22, 26, and 30 dB) were 4.1 (1.8), 4.1 (1.9), and 3.8 (1.9) dB for the sigmoid regression model, 5.5 (1.5), 6.0 (1.5), and 6.5 (1.5) dB for the exponential regression model, and 5.4 (1.5), 5.8 (1.7), and 5.9 (1.7) dB, respectively, for the linear regression model. The sigmoid regression model had the smallest mean RMSE value in all of these subsets.

Sigmoid Regression Model Analysis

The drop-off, inflection, and level-off points for a particular location are depicted in Figure 3. The median drop-off and inflection points, along with the rates of VF decay at these points for each subset group, are reported in the eTable in the Supplement.
Discussion

Glaucoma is a progressive disease, and it seems important to understand the course of its functional deterioration because it is measured perimetrically for both research and clinical care. Longitudinal VF testing provides data that have been used to model the progression of the disease. Studies have reported both linear and exponential regression models for fitting the perimetric data. Our findings show that a sigmoid regression model, with its natural upper and lower asymptotes, seems to offer a suitable alternative model for tests that traverse a large portion of the dynamic range of perimetric testing. To our knowledge, this is the first study to examine the course of progression from early glaucoma to near perimetric blindness with a sigmoid regression model.

For the analysis and comparison of these models, we combined 2 well-described patient databases with long-term follow-up and many serial VF tests. Because there is no statistical method to compare RMSE values, the model with the lowest RMSE value was considered the best fit for the subset of points examined. The residuals between each model were significantly different (P < .001). The large sample sizes account for the significant differences. The sigmoid regression model performed better than the linear and exponential regression models. These results support the hypothesis that the sigmoid regression model, with its natural asymptotes at perimetric normality and perimetric blindness, might reflect the pattern of perimetric measurements of glaucomatous visual loss from early to advanced stages of glaucoma.

The visual system is complex, which must be considered when interpreting the course of progression of a dis-

Table 2. Summary of Model Fit for 3 Regression Models for All VF Data and Subsets

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 40398)</th>
<th>Initial VF, dB*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 40398)</td>
<td>&gt;22 (n = 938)</td>
</tr>
<tr>
<td>Sigmoid RMSE (SD)</td>
<td>3.0 (1.7)</td>
<td>4.1 (1.8)</td>
</tr>
<tr>
<td>Sigmoid best fit, No. (%)</td>
<td>21339 (52.8)</td>
<td>686 (73.1)</td>
</tr>
<tr>
<td>Exponential RMSE (SD)</td>
<td>3.1 (1.8)</td>
<td>5.5 (1.5)</td>
</tr>
<tr>
<td>Exponential best fit, No. (%)</td>
<td>17263 (42.7)</td>
<td>171 (18.2)</td>
</tr>
<tr>
<td>Linear RMSE (SD)</td>
<td>3.1 (1.8)</td>
<td>5.4 (1.5)</td>
</tr>
<tr>
<td>Linear best fit, No. (%)</td>
<td>1796 (4.5)</td>
<td>81 (8.6)</td>
</tr>
</tbody>
</table>

Abbreviations: RMSE, root mean squared error; VF, visual field.

* Final VF mean was less than 10 dB.
ease such as glaucoma. The analysis of perimetric findings is confounded by the variability of VF data, the requirement for many tests to establish trends beyond the noise of the data, the requirement to confirm the results with repeated tests, and the inherent lack of adequate external validation.

Eight sample locations with initial sensitivity values greater than 30 dB and final sensitivity less than 10 dB are presented.
Both linear and exponential regression models have been used to fit glaucomatous VF deterioration because they are easy to apply and simple to interpret. These models assume that VFs deteriorate over time at a constant sensitivity or constant rate. Based on our findings, when following the behavior of a single test location with an initial high sensitivity and a low final value as a result of glaucomatous damage, the sigmoid regression model performed better than the exponential or linear models. When pointwise model fitting of visual sensitivities is performed against time, several assumptions are violated, including the nonindependence of the pointwise data in both time and space and the spread of the residual terms, which changes over time. Based on model fits according to disease severity, Lee et al showed that the nondecay exponential model fit the data better for early VF loss than did a linear model. These findings suggest that the loss of visual sensitivity from glaucoma is far from constant against time. According to our results, the sigmoid regression model might be used to represent the changes in the speed of deterioration over the course of the disease. Thus, different phases of disease deterioration are associated with different perimetric rates of deterioration.

It is important for health care professionals to determine the patients rate of disease progression and projections of that progression; it gives them the opportunity to offer adequate treatment to avoid sight-threatening VF loss while avoiding the cost and morbidity of unnecessary treatments. Different studies have shown that rates of progression vary widely among patients with glaucoma and that prior VF deterioration is a strong indicator of further deterioration. Caprioli et al have reported that the rate of VF deterioration is different in the same eye for the same patient in different locations. One patient typically has some regions of the VF in which the disease progresses slowly and other regions where it progresses rapidly. As our results suggest, it is also evident that the rates of deterioration change with the course of the disease. Because the sigmoid regression model allows the rate of change to vary over time, its model specification and model fitting are more complicated compared with those of other models. However, the sigmoid regression model provides a possibility to calculate the point of inflection of VF deterioration, the point at which the rate of decay is at its steepest, and the rate of VF deterioration at the corresponding point. Thus, the point of inflection of VF deterioration is the point in time when the acceleration of the sensitivity loss ends and deceleration begins. Furthermore, the rate of decay is allowed to vary at any point in time.

A floor effect is present during the final stages of the disease; measurements are noisier and may not reflect the actual physiologic status of the eye. A model such as the sigmoid function can provide health care professionals a tool to help analyze points at this stage.

For any 2 given points equidistant from the point of inflection, rotational symmetry is created. This rotational symmetry implies that the drop-off point is at the same distance from the point of inflection as the level-off point, but with opposite signs of acceleration. This symmetry does not necessarily reflect the actual behavior of VF deterioration, especially when treatment to slow the rate of progression is applied. After calculation of the drop-off and inflection points, their rates can be obtained and used to detect areas of the VF that deteriorate faster than other regions or may be used to explore the course of progression for a particular area of the VF.

The limitations of this study must be considered. Each point was analyzed independently from its adjacent points. The sigmoid regression model, like all other perimetric models, does not take this issue into consideration. Only locations with initial high sensitivities and low final sensitivities were selected for analysis. Although these locations represent a subset, they were selected to represent the course of the disease across the entire perimetric measurement range. In addition, each eye required many VF examinations to regress the point-
wise model owing to the complexity of the sigmoid function. Eyes included in the study were receiving treatment, so this deterioration is undoubtedly influenced by treatment.

The natural history of glaucoma consists of several stages, including progressive damage,VF loss, and, in a substantial minority of patients, blindness. It is expected that both structural and functional factors are related in the natural course of the disease, because both are determined by a common pathophysiologic process: the death of retinal ganglion cells with loss of related axons and their support.19,20 The association between the rate of ganglion cell death and the rate of VF loss for a given stage of disease has not been completely described and likely changes as the disease progresses. Our findings on the behavior of VF deterioration over time may serve as an interesting starting point to better address this association. Additional research to validate the sigmoid regression model is planned. The tails of the distribution of a sigmoid regression are symmetric, but the distributions may be skewed; applying a Weibull distribution model to our data may provide a better fit. We also plan to find the best model fit in a 1/Lambert scale.

Conclusions

A pointwise sigmoid regression model provided the best fit for perimetric progression among a large number of VF locations, particularly in a subset of VF locations that, on longitudinal follow-up, traverse a large range of perimetric sensitivities from near normal to near perimetric blindness. These results support the concept that the measured behavior of glaucomatous VF loss to perimetric blindness is nonlinear and that its course of deterioration may change with the course of disease.

REFERENCES