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Predicting Vision-Related Disability in Glaucoma

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Purpose: To present a new methodology for investigating predictive factors associated with development of vision-related disability in glaucoma.

Design: Prospective, observational cohort study.

Participants: Two hundred thirty-six patients with glaucoma followed up for an average of 4.3±1.5 years.

Methods: Vision-related disability was assessed by the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) at baseline and at the end of follow-up. A latent transition analysis model was used to categorize NEI VFQ-25 results and to estimate the probability of developing vision-related disability during follow-up. Patients were tested with standard automated perimetry (SAP) at 6-month intervals, and evaluation of rates of visual field change was performed using mean sensitivity (MS) of the integrated binocular visual field. Baseline disease severity, rate of visual field loss, and duration of follow-up were investigated as predictive factors for development of disability during follow-up.

Main Outcome Measures: The relationship between baseline and rates of visual field deterioration and the probability of vision-related disability developing during follow-up.

Results: At baseline, 67 of 236 (28%) glaucoma patients were classified as disabled based on NEI VFQ-25 results, whereas 169 (72%) were classified as nondisabled. Patients classified as nondisabled at baseline had 14.2% probability of disability developing during follow-up. Rates of visual field loss as estimated by integrated binocular MS were almost 4 times faster for those in whom disability developed versus those in whom it did not (−0.78±1.00 dB/year vs. −0.20±0.47 dB/year, respectively; $P < 0.001$). In the multivariate model, each 1-dB lower baseline binocular MS was associated with 34% higher odds of disability developing over time (odds ratio [OR], 1.34; 95% confidence interval [CI], 1.06−1.70; $P = 0.013$). In addition, each 0.5-dB/year faster rate of loss of binocular MS during follow-up was associated with a more than 3.5 times increase in the risk of disability developing (OR, 3.58; 95% CI, 1.56−8.23; $P = 0.003$).

Conclusions: A new methodology for classification and analysis of change in patient-reported quality-of-life outcomes allowed construction of models for predicting vision-related disability in glaucoma. *Ophthalmology 2018;125:22-30 © 2017 by the American Academy of Ophthalmology*

Glaucoma is estimated to affect more than 80 million people by 2020, making it the leading cause of irreversible blindness in the world.[1] As a major cause of visual loss, glaucoma potentially can affect several aspects of quality of life (QoL) and can impair performance on a broad array of activities of daily living, such as reading, walking, and driving.[2–9] Because currently available treatments for glaucoma may have side effects, knowledge of when and how glaucoma produces disability is important, because aggressiveness of treatment should be dictated by the need to slow down the rate of visual loss to prevent disability.

Disability in glaucoma frequently has been evaluated by patient-reported questionnaires, such as the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25).[10] This questionnaire contains a set of 25 questions designed to assess the dimensions of self-reported vision-target health status that are relevant for patients with chronic eye diseases. Interpretation of NEI VFQ-25 results usually has relied on scores that summarize patients' responses to the questionnaires and that are supposed to represent the overall degree of vision-related disability. Previous investigations have shown significant relationships between visual field assessment by standard automated perimetry (SAP) and NEI VFQ-25 scores.[11–13] A recent study showed that both baseline visual field severity and rates of visual field loss over time were associated with the magnitude of change in NEI VFQ-25 scores over time in patients with glaucoma.[14] Each 1-dB change in binocular SAP mean sensitivity per year was associated with a change of 2.9 units per year in an NEI VFQ-25 Rasch-calibrated score during the follow-up period.

Despite the previously reported associations between NEI VFQ-25 results and SAP, translating these findings into clinical practice has been difficult. To make treatment decisions, a clinician often is interested in being able to translate current clinical findings, such as rate of visual field loss, into an estimate of the risk that visual disability will

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occur in the future. For example, if the risk of future disability is high for the current rate of change, more aggressive treatment generally is indicated to slow down progression. However, if the risk is low, a conservative approach may be chosen, considering benefits and potential side effects of the available treatment options.

In this study, we investigated the relationship between baseline and rates of visual field deterioration and risk of future development of vision-related disability in glaucoma. We present an innovative approach for analysis of NEI VFQ-25 data that allowed us to derive a predictive model relating SAP results to the risk of future vision-related disability to assist in clinical decision making in glaucoma.

Methods

Participants from this study were included in a prospective, longitudinal study designed to evaluate functional impairment in glaucoma conducted at the Visual Performance Laboratory of the University of California, San Diego. The institutional review board approved the methods, and written informed consent was obtained from all participants. The study adhered to the Health Insurance Portability and Accountability Act, and all study methods complied with the Declaration of Helsinki guidelines for human subject research.

During follow-up, patients underwent comprehensive ophthalmologic examinations, including review of medical history, visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, gonioscopy, dilated funduscopic examination, stereoscopic optic disc photography, and SAP using 24-2 Swedish interactive threshold algorithm standard (Carl Zeiss Meditec, Inc., Dublin, CA). Only patients with open angles on gonioscopy were included. Patients were excluded if they demonstrated any other ocular or systemic disease that could affect the optic nerve or the visual field. Visual fields were excluded if they had more than 33% fixation losses or more than 15% false-positive errors. All visual fields were evaluated by the University of California, San Diego, Visual Field Assessment Center and were excluded in the presence of eyelid or rim artifacts, fatigue effects, or evidence that the visual field results were caused by a disease other than glaucoma.[15]

Study Participants

To be included, participants had to have a diagnosis of glaucoma at baseline based on the presence of repeatable (at least 2 consecutive) abnormal SAP results at baseline with corresponding optic nerve damage in at least 1 eye. Abnormal SAP results were defined as a pattern standard deviation with $P < 0.05$, glaucoma hemifield test results outside normal limits, or both.

Participants completed the NEI VFQ-25 questionnaire at baseline and at the end of follow-up. For the duration of follow-up, participants also were tested with SAP Swedish interactive threshold algorithm 24-2 at approximately 6-month intervals. To evaluate binocular visual field loss, sensitivities of the monocular SAP threshold sensitivities of the right and left eyes were used to calculate an integrated binocular visual field, according to the binocular summation model described by Nelson-Quigg et al.[16] Evaluation of rates of visual field change was performed by fitting ordinary least squares linear regressions using the mean sensitivity (MS) of the integrated binocular visual field over time. Rates of change also were obtained for mean deviation (MD) values for the better and worse eyes, classified according to baseline MD. During follow-up, participants were treated at the discretion of the attending ophthalmologist.

25-Item National Eye Institute Visual Function Questionnaire

Vision-related QoL was assessed by NEI VFQ-25 questionnaires.[10] The NEI VFQ-25 consists of 25 questions measuring overall vision, difficulty with near-vision and distance activities, ocular pain, driving difficulties, limitations with peripheral vision and color vision, social functioning, role limitations, dependency, and mental health symptoms. For the present study, items related to dependency, mental health, and role limitations were excluded from the analysis of NEI VFQ-25 data because they have been shown previously to belong to a separate socioemotional dimension not directly related to visual functioning.[14,17,18] In addition, the 2 items belonging to the subscale of ocular pain also were excluded because ocular pain likely would produce changes in QoL that are not related directly to those produced by loss of vision resulting from glaucoma. The remaining 14 questions were used to assess vision-related disability status based on the NEI VFQ-25. This approach has been used in several previous publications investigating the relationship between SAP and vision-related QoL measured by the NEI VFQ-25.[14,18–21]

Latent Transition Analysis

A latent transition analysis (LTA) model was used to characterize vision-related disability from NEI VFQ-25 results and to investigate the probability of developing disability during follow-up. An LTA model is an extension of a latent class model to longitudinal data.[22] The term *latent* means that an error-free latent variable is postulated. This latent variable corresponded to vision-related disability, which is not measured directly. Instead, it is measured indirectly by the NEI VFQ-25 questionnaire items. Unlike the latent variable, the observed variables are subject to errors. In latent class analysis, the latent classes are defined by the criterion of conditional independence. This means that, within each latent class, each variable is statistically independent of every other variable. That is, latent classes are defined such that, if one removes the effect of latent class membership on the data, all that remains is randomness (understood here as complete independence among measures). Previous work has argued that this criterion leads to the most natural and useful groups.[22]

There were 2 time points, corresponding to baseline and the end of follow-up, and only the questionnaires obtained at those 2 time points were considered. At each time point, a categorical latent class variable (disability) was postulated. Participants then were classified into 2 mutually exclusive latent classes, disabled and nondisabled, based on the results of the NEI VFQ-25 questionnaires at each time point. The model estimated the probability of membership to each class at each time point based on the questionnaire responses and assigned the individual to the class with highest probability of membership. The LTA model was used to study the probability of transitioning between classes. For example, a participant who is classified as nondisabled at baseline could stay as nondisabled at the end of follow-up or could transition to the disabled class. As hypothesized in this study, a transition to the disabled state would have a high chance of happening if the participant showed a large amount of visual field loss during follow-up. Conversely, a participant who is disabled at baseline could stay disabled, but alternatively could become nondisabled at follow-up. Although glaucomatous visual field loss is not expected to improve, a transition to a nondisabled state could happen, for example, if the participant finds himself less limited by the disease or from an intervention that could improve vision, such as cataract surgery.

Although models with larger numbers of latent classes would be possible, the model with 2 classes at each time point had the best fit, as assessed by Bayesian information criterion.[23] The entropy of the model was 0.889. The entropy measures the uncertainty in