Graefes Arch Clin Exp Ophthalmol
DOI 10.1007/s00417-016-3573-x

GLAUCOMA

Predicting conversion to glaucoma using standard automated perimetry and frequency doubling technology

Genichiro Takahashi[1] · **Shaban Demirel**[2] · **Chris A. Johnson**[3]

Received: 19 August 2016 / Revised: 12 December 2016 / Accepted: 22 December 2016

Abstract
Purpose To test the hypothesis that development of glaucomatous visual fields can be predicted several years earlier from prior visual field information.
Methods One-hundred and seven eyes with glaucomatous optic neuropathy ($n = 47$ eyes) or which were suspicious for glaucoma ($n = 60$) were prospectively enrolled in a longitudinal study. Visual fields were evaluated on an annual basis using standard automated perimetry (SAP), the original version of frequency doubling technology (FDT) perimetry, and a custom version of FDT that used the 24-2 stimulus pattern. All SAP fields were within normal limits at the initial visit. When the SAP glaucoma hemifield test was 'outside normal limits' *or* the pattern standard deviation probability was worse than the lower 5th percentile *or* more than two clustered locations at the $p < 0.05$ level were present on the pattern deviation probability plot, an eye was defined as being abnormal. We used a classification tree analysis to predict which eyes would convert, using only baseline test results.
Results Classification trees that were constructed using only baseline data had excellent specificity (near 100%) but worse sensitivity (25–50%) for predicting which eyes would convert during follow-up.
Conclusions Predictive information is present in visual field results, even when they are still within normal limits.

Keywords Visual fields · Glaucoma · Frequency doubling · Progression

✉ Chris A. Johnson
chris-a-johnson@uiowa.edu

[1] Department of Ophthalmology, Jikei University, School of Medicine, Katsushika Medical Center, Tokyo, Japan

[2] Discoveries in Sight Research Labs, Devers Eye Institute, Portland, OR, USA

[3] Department of Ophthalmology and Visual Sciences, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242-1091, USA

Introduction

It has been reported that histologically the number of retinal ganglion cells (RGCs) may be substantially reduced before glaucomatous visual field loss becomes detectable with standard automated perimetry (SAP) [1, 2]. Some have suggested that this may be due, at least in part, to different scales used for measurement of optic nerve structure and measures of visual function [3–5]. However, early detection and appropriate treatment can prevent or slow the development of glaucomatous damage [6, 7]. It seems reasonable therefore to search for more sensitive functional tests that may be able to detect the earliest signs of glaucomatous functional loss.

Various investigators have proposed functional tests that may detect glaucomatous damage at an earlier stage than SAP. One such test is short wavelength automated perimetry (SWAP), which utilizes a short wavelength stimulus upon a bright yellow background to assess functioning of the short wavelength sensitive mechanisms [8–12]. However, recent findings suggest that SWAP is not able to detect glaucomatous visual field loss earlier than SAP [13, 14], although another report indicates that both SAP and SWAP can provide early detection of glaucomatous visual field damage, and there is only partial overlap in those patients that demonstrate both SAP and SWAP deficits early in the disease process [15].

Another promising test is frequency doubling technology (FDT) perimetry [16, 17] (Carl Zeiss Meditec, Dublin, CA, USA and Welch Allyn, Skaneateles, NY, USA). FDT

Published online: 21 January 2017

perimetry presents low spatial frequency sinusoidal stimuli (<1 cycle/degree) that undergo high temporal frequency contrast modulation (>15 Hz flicker). It has been claimed that these stimuli are predominantly detected by magnocellular retinal neurons or Y-type cellular mechanisms [16–18], although recent findings suggest that this effect is not mediated solely by the magnocellular pathways [19–21]. Alternatively, recent neurophysiological [22–24] and psychophysical [25] studies provide evidence for Y-type cellular responses that may be responsible for the frequency-doubling effect. However, in this view, both FDT and SWAP have been reported to detect glaucomatous damage at an earlier stage than SAP [13, 16].

In the present study, we have examined the ability of three different types of perimetry to predict the development of early-stage glaucomatous visual field loss defined using SAP. Two types of FDT perimetry, the original version and a custom version that presents stimuli at 54 locations using the 24-2 presentation pattern [26], were used along with SAP. We applied a form of classification tree analysis to see if it was possible to predict who would develop glaucomatous visual field damage. We have used this analysis to test the hypothesis that predictive information exists in visual fields at a time when they are still within normal limits on SAP.

Materials and methods

All participants in this research were given detailed explanations of the study requirements and the duration of the tests, and they provided their written informed consent before study entry. All protocols were in accordance with the tenets of the Declaration of Helsinki and were approved by the Legacy Health Systems institutional review board for the protection of human subjects in research.

The present study was designed as a prospective, longitudinal investigation. Only data from individuals who had a baseline assessment and three annual follow-up visits (four total visual fields) were analyzed. We compiled data from 107 eyes of 75 participants who met this requirement. Although the two eyes of the same individual are correlated (including glaucoma patients and glaucoma suspects), we were concerned with the ability to predict visual field conversion to glaucoma per individual eye rather than per participant. All eyes were assigned to one of two groups depending on their ocular findings and risk of developing glaucoma. The first group consisted of participants who had evidence of glaucomatous optic neuropathy (GON group), but no abnormality evident with SAP testing. Two fellowship-trained glaucoma specialists (George A. Cioffi, M.D. and Steven L. Mansberger, M.D.) determined the presence of GON by examining stereo optic nerve head photographs. A description of the procedures used for determination of glaucomatous optic disc features has been provided in a previous publication [27]. The second group (suspect group) included eyes that did not have GON and did not have abnormal SAP results, but had at least two recognized risk factors for glaucoma (e.g., glaucomatous family history, history of vasospasm, advancing age, African-American race, ocular hypertension, other eye with glaucoma). There were 47 eyes (38 individuals) in the GON group and 60 eyes (45 individuals) in the suspect group. In summary, all participants in both groups had normal SAP results, but group 1 had evidence of glaucomatous optic neuropathy and group 2 did not have any evidence of glaucomatous optic neuropathy.

FDT perimetry using the original device was conducted using the modified binary search (MOBS) procedure in combination with the N-30 stimulus pattern [17, 24]. This perimeter and the type of stimulus it uses have been described in numerous other publications [19–21, 26–30].

Custom FDT perimetry (24-2 FDT) was conducted using an apparatus that was custom-built in our laboratory that is referred to as Quadravision. This apparatus uses an array of four 21-inch monochrome monitors, each run at 1,280 × 1,600 pixel resolution, that were optically combined using front surface mirrors to cover the central 30-degree radius of the visual field. The equipment has been described in detail elsewhere [26]. A set of stimulus locations identical to the 24-2 pattern of the Humphrey perimeter was employed (54 locations throughout the central 24-degree radius arranged on a 6-degree grid that straddles the horizontal and vertical midlines). Unlike the commercial version of the original FDT perimeter, stimuli were 4° diameter squares of 0.5-cycle/degree vertical sinusoidal gratings undergoing squarewave counterphase flicker at 18 Hz (36 alternations/second). The average stimulus luminance was equal to the luminance of the background at 50 cd/m^2 and the device was calibrated using a Photo Research Spectra Pritchard Model 1980 A photometer and a Photo Research Spectrascan Model PR 670 Photometer/Radiometer. Contrast thresholds for detection were measured under the control of a modified binary search (MOBS) algorithm [17, 28]. SAP was performed using the Humphrey Field Analyzer II (Model 750; Carl Zeiss Meditec, Dublin, CA, USA) 24-2 SITA standard procedure using standard test parameters [31, 32].

A SAP visual field was considered abnormal if either the Glaucoma Hemifield Test (GHT) was "outside normal limits", the pattern standard deviation (PSD) probability was worse than the lower bound of the 95% confidence limits, *or* greater than two clustered locations were worse than the 5% level on the pattern deviation (PD) probability plot. These values were based on an age-adjusted STATPAK-like analysis procedure that we developed, based on testing 100 healthy participants with normal vision between the ages of 18 and 85. All participating eyes had SAP visual fields that were within normal limits at the baseline visit.

We established two definitions of conversion to perimetric glaucoma. One definition was used where an eye was considered to have converted the first time it produced an abnormal SAP field (an individual suspected change), and a second definition where an eye was considered to have converted when it produced a second abnormal SAP field (confirmation of a suspected individual change).

Statistical analysis was performed using the R software package [33] (version 1.8.1, The R Foundation, http://www.r-project.org). R is open source software available at no cost under the terms of the Free Software Foundation's GNU General Public License (http://www.gnu.org/ & http://www.r-project.org/index.html). To perform classification tree analysis, R is used in concert with an 'rpart' package (a contraction of recursive partitioning, version 3.13, Terry Therneau and Beth Atkinson, R translation by Brian Ripley) which facilitates construction, analysis and display of tree models. Classification and regression trees have been described by Breiman et al. [34]. A detailed description of the workings of the technique is beyond the scope of this paper, and interested parties should consult the original manuscript. Briefly, classification trees are a form of binary recursive partitioning. During this procedure, a dataset is divided into many subgroups by applying multiple successive splits based on predictor variables. All splits are binary in nature so that cases must go in one of two directions. The aim in this case is to produce a set of predictor variables, and cut-points associated with them, that can best split the data into converting (progression) and non-converting (stable) eyes while minimizing the number of misclassified cases. All the predictor variables used are shown in Table 1. The final subgroups were classified by the procedure, based on the most likely finding for eyes that appear in that subgroup (i.e., converted or not converted). It is then possible to examine the 'hits' and 'misses' and thus calculate the sensitivity and specificity of the classification tree. The process can be considered as generating an upside-down tree where each fork has two branches. Cases are processed through the tree with the direction taken at each fork determined by questions applied to the predictor variables. Note that because the decision tree is recursive, the same variable can be incorporated in separate sections of the model with different values. It is well recognized that statistical models almost always perform best with the dataset used to create them. During classification tree analysis it is possible to over-specify the classification tree until perfect performance is achieved by assigning each eye a personalized set of decision rules. Such a tree would perfectly describe the dataset used to produce it, but would not be suited for use with other datasets. Alternatively, it is possible to guide the tree-construction algorithm so that it penalizes complex sets of decision rules in favor of more simple schemes. Alternatively, a maximum depth of tree growth can be set by limiting the number of levels of branching that can occur and by specifying the minimum size of a branch before it can be considered for further splitting. Another method of choosing the optimum classification tree uses a cross-validation technique that is meant to estimate how the tree model will perform when applied to an independent dataset. Perhaps the best method for evaluating the validity and generalizability of the model is to see how well it performs when applied to an independent data set of patients who have been followed longitudinally with these procedures.

Table 1 Predictor variables used (○) or not used (×) during classification tree construction

Predictor	Perimetry test		
	SAP	Original FDT	24-2 FDT
Age	○	○	○
Gender	○	○	○
Group	○	○	○
MD	○	○	○
PSD	○	○	○
# of TDPP points @	5%, 2%, 1%, & 0.5%	5%, 1%	5%, 2%, 1%, & 0.5%
# of PDPP points @	5%, 2%, 1%, & 0.5%	×	5%, 2%, 1%, & 0.5%
GHT	○	×	○

SAP = standard automated perimetry (24-2 SITA standard procedure), Original FDT (original frequency doubling technology procedure using 19 visual field locations 10 degrees by 10 degrees throughout the central visual field), 24-2 FDT (procedure using 54 4 degree by 4 degree stimulus locations separated by 6 degrees bracketing the horizontal and vertical meridians), *MD* = mean deviation, *PSD* = pattern standard deviation, *GHT* = glaucoma hemifield test, *TDPP* = total deviation probability plot, *PDPP* = pattern deviation probability plot. In the rows for TDPP and PDPP, '5%' means that the number of points in the plot that were abnormal at the 5% level were included as a predictor variable

Results

The group mean ages (±1 standard deviation) at the initial visit were 54.2 ± 10.3 years (range: 26–75 years) in the GON group and 55.7 ± 11.2 years (range: 34–77 years) in the suspect group (no significant difference in baseline age between these two groups, unpaired $t = 0.7$, $p = 0.48$). Mean follow-up periods in the GON and suspect groups were 33.5 ± 6.6 and 34.9 ± 4.8 months respectively. Twenty-nine of 107 eyes (27%) converted based on the criterion of a single abnormal SAP field, whereas seven of 107 eyes (6.5%) converted based on the criterion of a subsequent confirmatory abnormal SAP field. Thus, 22 of 29 one-time abnormal eyes (75.9%) did not confirm by either method during the follow-up period (91.5% of the GON group and 95% of the suspect group). The difference between groups was not statistically significant (Pearson's chi-squared test, $\chi^2 = 0.11$, $p = 0.74$).

SAP results predicting SAP conversion

Figure 1 shows two classification trees (panel A for a single abnormality and panel B for a confirmed abnormality appearing on two successive exams), each constructed to split the data into converting and non-converting eyes, using baseline SAP data to do so. Note that no cross-validation, bootstrapping or resampling procedures were employed for these analyses. In the future, evaluation of an independent group of patients will be needed to establish the validity and generalizability of the model. The trees in panels A and B respectively were generated using the two conversion criteria as the target variable. Each eye in the cohort enters the tree at the top and the first splitting variable is examined. For the tree in panel A, this means that a case would take the left branch if the PSD was <1.59 but take the right branch otherwise. Thirty-two eyes had a PSD <1.59 and ended up in the terminal region on the left of panel A. Of these 32 eyes, 29 were non-converters and three were converters, as suggested by the fraction 29/3. The terminal region is classified as 'non converting' and labeled with a 0. This splitting procedure is followed down the tree using the variables and cutpoints printed on each branch. Table 2 displays the sensitivities and specificities for the classification trees shown in this figure. It can be seen that of all the potential predictor variables available to the tree model (Table 1) only three were included; PSD, MD and age.

FDT results predicting SAP conversion

Figure 2 is similar to the previous figure but uses baseline standard FDT results to split the dataset into converting and non-converting eyes based on the single (panel A) and confirming (panel B) conversion criteria. Table 2 displays the sensitivities and specificities for these classification trees. All three visual field procedures generated high specificities, particularly for the cases where a suspected progression was confirmed by a subsequent test procedure where specificities

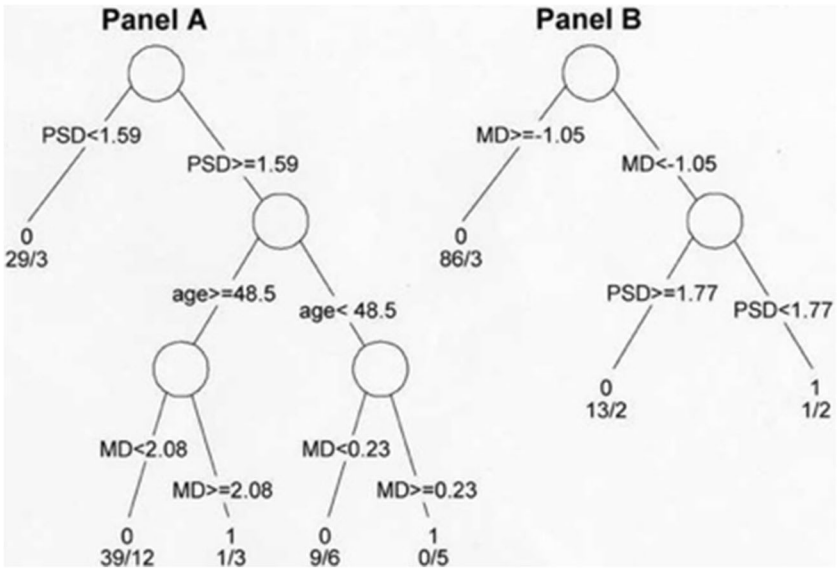

Fig. 1 Classification trees constructed to predict which eyes convert to perimetric glaucoma using only baseline SAP data to make this prediction. *Panel A* employs the liberal conversion criterion whereas *panel B* uses the conservative conversion criterion. At each branch (*circle*) a case goes right or left depending on the value of the predictor variable for that case. Terminal regions (not split further) report two numbers. The first is a 0 or a 1, which classifies the terminal as non-converting (0) or converting (1). The second number at each terminal region is a fraction of the form X/Y where X gives the number of non-converting eyes and Y gives the number of converting eyes that ended up in the terminal

Table 2 Sensitivities and specificities for the classification trees shown in Figs. 1, 2, and 3

Test and conversion criterion	Sensitivity	Specificity
SAP + single	27.6% (8/29)	98.7% (77/78)
SAP + confirming	28.6% (2/7)	99% (99/100)
Original FDT + single	55.2% (16/29)	88.5% (69/78)
Original FDT + confirming	28.6% (2/7)	99% (99/100)
24-2 FDT + single	17.2% (5/29)	100% (78/78)
24-2 FDT + confirming	28.6% (2/7)	100% (100/100)

Note that "confirming" and "single" refer to conversion based only on SAP results

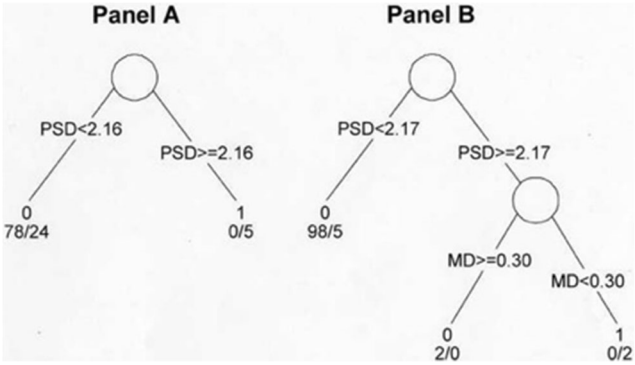

Fig. 3 As for Fig. 1 except that the trees were constructed using baseline results from 24-2 FDT perimetry as predictor variables

closely approached or equalled 100%. Sensitivity was lower, with differences for a single indication of progression, but all procedures reached approximately 28% sensitivity for confirmation of a suspected change. Only two of the potential predictor variables, PSD and age, were included in either of these two trees.

Figure 3 can be interpreted in the same way as the two previous figures, except that it uses baseline 24-2 FDT results to split the dataset into converting and non-converting eyes based on the single (panel A) and confirming (panel B) conversion criteria. Once again, Table 2 displays the sensitivities and specificities for these two classification trees. Pattern standard deviation and MD were the only predictor variables included in the tree model.

The average difference versus mean (Bland–Altman) [35] bias values for mean deviation (MD) and pattern standard deviation (PSD) (variation from zero or no difference) and 95% confidence intervals for standard automated perimetry (SAP), the original FDT device, and the 24-2 FDT procedure for all combinations of the four visits. The differences in results are minimal and the confidence limits are relatively small, except that the original FDT device findings showed much larger 95% confidence limits. It is likely that this is due to a smaller number of test locations and a different threshold estimation strategy. None of the comparisons has a slope that was meaningfully or significantly different from zero.

Discussion

In the present study, classification trees were generated that used only baseline data to predict conversion to glaucomatous visual field loss over a 3-year period. One of the advantages of classification trees is that they are non-parametric and that they allow complex interactions among predictor variables to be evaluated even when it would be difficult to express these interactions in traditional statistical models. Predictor variables can also appear in more than one location in the tree, allowing very subtle interactions between variables over

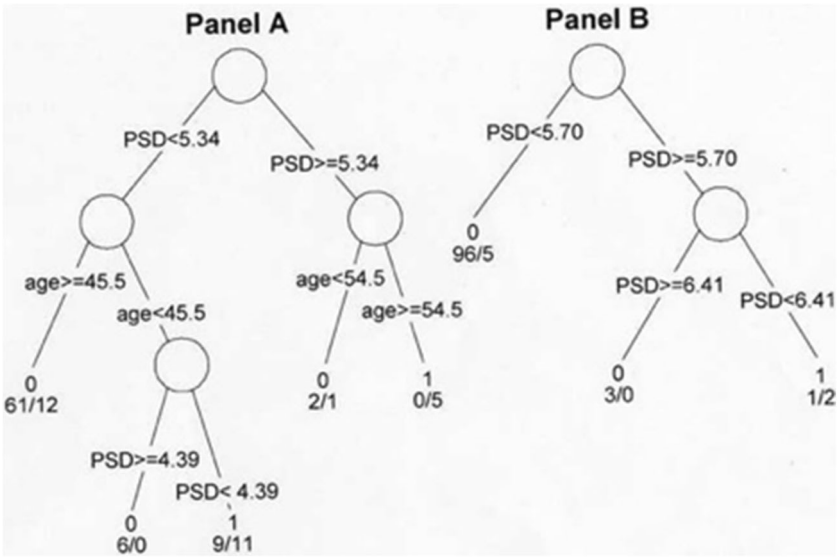

Fig. 2 As for Fig. 1 except that the trees were constructed using baseline results from standard FDT perimetry as predictor variables

different parts of their ranges to be investigated. For example, it can be seen in panel A of Fig. 1 that the variable MD is used at two different branch points. This suggests that the interpretation of MD may be dependent on the age of the subject, as the branch just above is split based on age. In a traditional statistical analysis, it would be more difficult to model this type of interaction where a single variable interacts differently with other variables depending on what sub range is being examined. Classification trees are a visually appealing way to depict these complex interactions, and allow for rapid determination of cases most likely to convert.

In the current analysis, good specificity but poorer sensitivity was achieved using baseline fields to predict which eyes would go on to convert. It should be noted that all eyes had SAP fields that were within normal limits at the baseline visit. This suggests that certain combinations of findings convey predictive information even if the individual components are within normal limits. This information may allow identification of 25–50% (Table 2) of converting eyes depending on the test used. Further investigation of methods to utilize this subtle predictive information should be pursued. Additionally, validation of this classification model should be based on evaluation of an independent data set.

When the results from the tests are compared, it is evident that the baseline results of 24-2 FDT and SAP both had similar ability to predict which SAP fields would convert. The baseline results of standard FDT examinations were better able to predict the converting eyes, but did so at the cost of slightly worse specificity. Note that the total deviation and pattern deviation values did not contribute to the classification, suggesting that the global indices are more predictive than pointwise values. In this view, mean deviation (MD) and the visual field index (VFI) are most commonly used to monitor visual field progression in glaucoma.

The current analysis has several potential weaknesses. Classification tree analysis generally works better with larger datasets and with a greater number of target events. Our use of this technique on data from 107 eyes with the confirming conversion criterion resulted in seven converters establishing the classification tree procedure. Also, statistical models tend to perform better with the dataset used to derive them, and the current results would need to be validated with independent data.

We also only have access to 3 years of follow-up for most eyes (baseline plus three annual follow-up visits), which limits the number of eyes that could convert. Additionally, paractitioners often use two visual fields rather than one to establish a baseline value. On the other hand, eye-care specialists are motivated to carefully monitor the visual status of patients so that any change in management can be instituted at the earliest time point, to reduce further deterioration of the visual pathways. Both the patient and the practitioner prefer to have relevant and reliable clinical information at the earliest possible time. This investigation represents a compromise between methodological and practical priorities for this analysis. The study is ongoing, and longer durations of follow-up are necessary. It would also be advantageous to include results from yearly optic nerve examinations as predictor variables, or perhaps to use such data as the conversion criterion so that all three perimetry tests could be compared on an equal footing. Currently, comparison of the three tests is also limited by the fact that one of them (SAP) was used to define conversion and study eligibility.

In summary, visual field results contain subtle predictive information that can be exploited even when the visual fields are still within normal limits. Classification trees have potential to help us utilize this information in a visually appealing manner. We are encouraged that specificity is high, since this would suggest that this model is unlikely to generate many false-positive results for predicting glaucomatous visual field progression. In the future, evaluating the predictive value of optic disc and retinal nerve fiber layer assessment and the combination of visual field and optic nerve results may provide much better findings for decision-tree analysis [36].

Compliance with ethical standards

Funding Welch Allyn provided financial support in the form of $ 36,000.00 funding. Welch Allyn had no role in the design or conduct of this research.

Conflict of interest During the time of this research the third author (CAJ) received research support from Welch Allyn and was a consultant for Welch Allyn. The first author (GT) and the second author (SM) have no financial interest related to this study or manuscript.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Institutional Research Board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Legacy Health Systems Institutional Review Board in Portland, Oregon.

Informed consent All participants in this study provided written informed consent prior to participating in this study, and received a copy of their consent form.

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