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Structural and Functional Parameters for Detecting a Glaucomatous Visual Field Defects

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ABSTRACT

Purpose : To investigate structural and visual field variables for detecting glaucoma. Methods : Standard automated perimetry (SAP), frequency-doubling technology (FDT) perimetry, and optic disc photography were performed in 180 patients (360 eyes). Further analysis was performed in 149 eyes of 89 patients in which classifications of the optic disc with the system of Nicolela et al by optic disc photographs were agreed on by at least 2 of the 4 observers. To determine their importance for detecting glaucoma, structural parameters, such as optic disc appearance and vertical cup-to-disc ratio, and the visual field parameters obtained through FDT and SAP were ranked with multivariate regression analysis (Classification and Regression Trees [CART]).

Results : Through the CART analysis, parameters for detecting glaucomatous visual field loss were ranked in descending order of contribution as follows : 2 or more pattern deviation locations of SAP less than the 2% probability level, 3 or more pattern deviation locations of FDT less than the 5% probability level, FDT pattern standard deviation values of 2.63 or more, and a cup-to-disc ratio of 0.7 or more.

Conclusions : Glaucoma can be detected more efficiently and systematically by combining structural and visual field parameters in their order of importance.

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Key words : classification of glaucomatous optic nerve appearance, standard automated perimetry, frequency-doubling technology perimetry, pattern deviation, pattern standard deviation

INTRODUCTION

It is often difficult to detect early glaucoma through either standard automated perimetry (SAP) testing or structural assessment alone since morphological changes occur prior to SAP testing[1,2] and structural assessment is subjective with a high variability[3–5]. This problem is widely recognized, and the currently accepted definition of glaucoma requires the presence of a glaucomatous field loss in conjunction with corresponding optic disc or retinal nerve fiber layer (RNFL) defects. Although many reports have suggested a relation between the characteristics of the visual field defects and structural damage (e.g., shape change and thinning of the neuroretinal rim, localized and diffuse deepening and widening of the optic cup, and RNFL defects) observed with optic disc photography, confocal scanning laser ophthalmoscopy, and confocal scanning laser polarimetry[6–19], how to systematically combine and assess these parameters

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remains unclear.

We performed a prospective cross-sectional study to investigate the importance and optimal order of structural and visual field parameters for detecting glaucoma. To classify the optic disc's appearance objectively regardless of specific instruments used, we used the optic disc classification method of Nicolela et al. [6,7]. We evaluated the following structural parameters of the optic disc:the vertical cup-to-disc ratio (C/D ratio), RNFL defects, peripapillary atrophy (PPA), and optic disc hemorrhage (DH). Data from frequency-doubling technology (FDT) perimetry, which indicates early visual field loss[20], and standard automated perimetry (SAP) were evaluated as functional parameters.

Methods

Visual field testing and color optic disc photography were performed in 180 consecutive patients to evaluate glaucoma or suspected glaucoma at the Glaucoma Service of The Jikei University Hospital. Patients with suspected glaucoma included those with eyes having SAP visual fields within normal limits, however, they had recognized risk factors for glaucoma (e.g., family history of glaucoma, advanced age, ocular hypertension, glaucoma-like disc). Patients were ineligible if they had a history of diabetes or systemic disease, ocular disease other than glaucoma, or surgery or were receiving any medication known to affect the visual field. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained in advance from all subjects.

SAP testing (Humphrey Field Analyzer II 750, Humphrey/Zeiss Systems, Dublin, CA, USA) was performed with conventional test procedures (Goldmann size III-stimulus, 31.5 apostilbs white background, 30-2 full-threshold strategy), an optimal lens correction for the test eye, and occlusion of the fellow eye with an eye patch. FDT perimetry testing (Humphrey Systems and Welch Allyn, Skaneateles, NY, USA) was performed with a full-threshold N-30 stimulus presentation pattern without near visual acuity lens correction. Visual fields were excluded if any abnormal reliability factor was present (fixation loss >20%, false-positive rate >33%, and false-negative rate >33%).

Color photographs of the optic disc were taken of all subjects (with dilated pupils) within 6 months before or after visual field testing. Four observers unaware of the subject's clinical and visual field information independently reviewed each photograph according to the classification of Nicolela et al.[6,7]. We also used Anderson's criteria[21] to define the minimum visual field abnormality: 1) a glaucoma hemifield test (GHT) outside normal limits; 2) a pattern standard deviation (PSD) less than the 5% probability level; and 3) 3 or more pattern deviation (PD) nonedge clusters less than the 5% probability level, with 1 of these points less than the 1% probability level.

Multivariate analysis[22] was performed (Classification and Regression Trees [CART], version 3.6, Salford Systems, San Diego, CA, USA), with the target variable being the presence of visual field loss (SAP conversion defined by Anderson's criteria) and the independent variables being the structural and visual field parameters shown in Table 1. A PSD probability level of SAP and a GHT classification of "outside normal limits" were not supplied in the model, because these were features used in our defini-

Table 1. Parameters used for multivariate analysis

group (POAG, NTG, suspected glaucoma), gender, age, eye (right, left)
Optic disc photograph
optic disc classification proposed by Nicolela et al., RNFL defect, DH, PPA, C/D ratio (1～3*)
FDT
MD value, MD probability level, PSD value, PSD probability level, number of TD, PD abnormal points worse than the 5, 2, 1, 0.5% probability level
SAP
MD value, MD probability level, PSD value, number of TD, PD abnormal points worse than the 5, 2, 1, 0.5% probability level Classification of GHT (excluded "outside normal limits")

POAG=Primary open angle glaucoma, NTG=Normal tension glaucoma, MD=mean deviation, TD=total deviation, PD=pattern deviation

*: 1=optic cup-to-disc ratio (C/D)<0.5, 2=0.5<=C/D<0.7, 3=C/D>=0.7

tion of abnormality and would have produced circular logic in the modeling. Because the definition of abnormality based on the PD plot had a clustering requirement, the number of locations on the PD plot at a given probability level might be entered into the model. However, there was no information regarding clustering within these parameters; therefore, circular logic would be avoided. Sensitivity, specificity, and a receiver operating characteristic (ROC) curve were also calculated. Furthermore, stepwise logistic regression analysis was performed (Intercooled Stata 5.0, Stata Inc., College Station, TX, USA), and the results were compared with those produced by CART.

Results

1. *Classification of optic nerve appearance*

Of the 360 eyes in 180 patients, 149 eyes in 89 patients (40.5%) in which at least 2 observers agreed on the classification of optic nerve appearance were entered into analysis. Fifty-one of these subjects were men and 38 were women and were aged 52.6± 12.2 years (mean±SD; range: 25-77 years) when the study began. Table 2 shows the classification of optic disc appearance according to the classification of Nicolela et al.[6,7].

2. *Classification of glaucoma and visual field defects*

Twenty-four eyes (16.1%) had primary open angle glaucoma, 46 eyes (30.9%) had normal tension glaucoma, and 79 eyes (53.0%) had suspected glaucoma. The mean deviation value of all subjects was −4.04±5.54 dB (mean±SD).

Table 2. Classification of optic nerve appearances*

Classification	No. (%)
focal ischemic discs	29 (19.5)
myopic glaucomatous discs	49 (32.9)
senile sclerotic discs	17 (11.4)
generalized enlargement	54 (36.2)

*n=149, Results of the classification proposed by Nicolela et al.[6,7].

3. *C/D ratio, RNFL defect, PPA, DH*

The C/D ratio was less than 0.5 in 38 eyes (25.5%), 0.5 or greater and less than 0.7 in 29 eyes (19.5%), and 0.7 or greater in 82 eyes (55.0%). Two eyes (1.3%) had an RNFL defect, 59 eyes (39.6%) had PPA, and 1 eye (0.7%) had a DH.

4. *Multivariate regression model*

CART analysis

A PD of SAP less than the 2% probability level was determined to be the factor with the highest contributory ratio, and visual field loss could be detected when there were 2 or more PD locations less than the 2% probability level (Fig. 1). If there was only 1 PD location of SAP less than the 2% probability level, then visual field loss could still be detected if

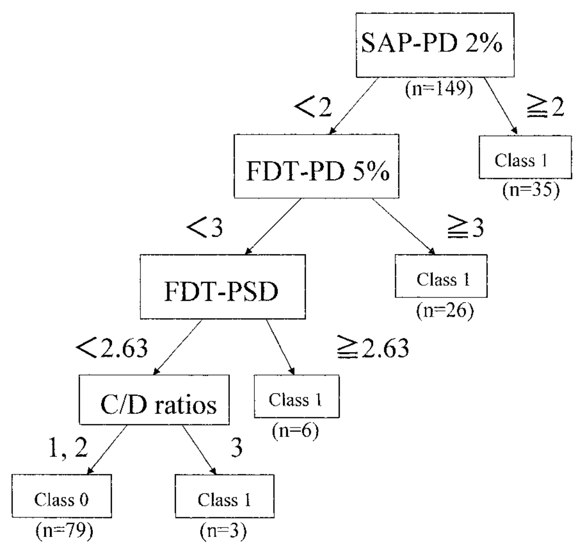

Fig. 1. When all structural and functional variables were used for classification and regression tree modeling, we found that a parameter of 2 pattern deviation (PD) locations of SAP less than the 2% probability level produced the best performance. Abbreviations: SAP-PD 2%: the number of PD locations of SAP less than the 2% probability level; FDT-PD 5%: the number of PD locations of FDT perimetry less than the 5% probability level;FDT-PSD, the value of pattern standard deviation of FDT. C/D ratio: 1=<0.5; 2=>0.5 and <0.7; 3≥0.7. Class 0=no conversion by the definition of visual field abnormality; class 1= conversion by the definition of visual field abnormality.

Table 3. Actual and predicted classes

		Predicted class		Total
		Class 0	Class 1	
Actual class	Class 0	79	8	87
	Class 1	0	62	62
	Total	79	70	149

Data shown are numbers of eyes.
Class 0=no converter by our definition, Class 1=converter by our definition, Predicted class=classification provided by CART, Actual class=Classification provided by our definition.

there were 3 or more PD locations of FDT less than the 5% probability level. If there were less than 3 PD locations of FDT less than the 5% probability level, visual field loss could still be detected when the PSD of FDT was 2.63 or more. Lastly, if the PSD was less than 2.63, visual field loss could still be detected when the C/D ratio was 0.7 or more.

The relation between the presence of visual field loss detected with the definition used in the present study (hereafter, "our definition") and the detection of visual field loss with CART is shown in Table 3. With our definition, visual field loss was present in 62 of 149 eyes and absent in 87 eyes. With these results as a gold standard, CART analysis was correct in 79 of the 87 eyes without visual field defects and in all 62 eyes with visual field defects. The sensitivity of CART analysis was 100%, specificity was 91.0%, and the area under the ROC curve was 97.7%.

Stepwise multivariate logistic regression model

Stepwise logistic regression analysis showed that the presence of visual field loss could be detected with several parameters: PSD of FDT, the number of abnormal total deviation locations of SAP less than the 5% probability level, the number of abnormal PD locations of SAP less than the 1% probability level, and C/D ratios ($p < 0.01$).

Discussion

By performing CART analysis we determined that the following parameters, in descending order, contributed most to the detection of glaucoma: 2 or more PD locations of SAP less than the 2% probability level, 3 or more PD locations of FDT less than the 5% probability level, a PSD of FDT of 2.63 or more, and a C/D ratio of 0.7 or more. Interestingly, visual field defects could be detected with CART even when visual field indices were within normal limits. The importance of these visual field parameters has also been shown with short wavelength automated perimetry (SWAP)[23]. A parameter of 3 or more PD locations of FDT less than the 5% probability level is similar to the early stage in a classification system proposed by Sponsel et al.[24] based on FDT results. In addition, our results confirm that increasing PD and PSD values are signs of increasing localized field loss[21].

Several recent studies have examined relations between structural and functional findings and the detection of glaucoma[6−19]. A study by Vihanninjoki et al.[15] examined the optimal combination of structural parameters using confocal scanning laser polarimetry and functional parameters. This study found that the total overall RNFL score provided the greatest separation between glaucomatous and nonglaucomatous eyes when structural and functional parameters were considered. However, only the C/D ratio from among the structural parameters was selected as an independent structural parameter that contributed to discrimination of the dependent measure in CART. Stepwise logistic regression analysis also showed that the C/D ratio was significantly related to visual field loss. Possible reasons why DH and RNFL defects were not selected in our study are that DH had not yet developed when optic disc photography was done and that photographs in few patients clearly showed an RNFL defect, suggesting that disease types and stages have an influence and that there is difficulty in finding a high level of agreement among observers. In previous studies, the agreement between structural damage and visual field damage was investigated with multivariate analysis or with area under the ROC curve and quantitative imaging techniques, such as a confocal scanning laser ophthalmoscopy[15−17]. The sensitivity, specificity, and the area under the ROC curve that we obtained in the present study were similar to those in previous studies.

Although the rate of agreement between at least 2 observers in our study was less than 50%, this rate was similar to that in a study by Nicolela et al.[25]. With this classification method, optic disc appearance was easily classified into 4 types with optic disc photographs. Optic disc photography is simple, and funduscopic cameras are widely available. This method may therefore be suitable for the primary care setting as well as general clinical practice. Meanwhile, because the diagnostic accuracy and inter-observer agreement of optic disc photographs alone are poorer than those of quantitative imaging techniques[4,5], this method of evaluation should be combined with visual field testing. This classification method must be further refined to decrease its inherent variability and to increase its ability to detect persons at risk for glaucoma.

The CART analysis used in the present study is a statistical algorithm developed in 1973 and actualized with computer software in the early 1980s[22]. In CART, samples are multiply stratified through repeated binary branching based on a series of independent variables in descending order of their contribution to obtain better discrimination of the target variable. By expressing the results as a classification tree (Fig. 1) in which the independent variables are selected in the order of their contribution, a calculated classification is produced, and the complicated results can be shown in a visual form. In medicine, CART is used to prioritize disease information and optimize treatment for patients hospitalized for emergency treatment of cardiac diseases[26,27]. CART is also used for marketing and environmental control. Because results of CART analysis would clearly show the relation between a target variable and independent variables with prioritization and reference values, we believed that CART could be used to analyze visual field loss.

In summary, the present study demonstrates that glaucoma can be detected more efficiently and systematically by combining structural and visual field parameters in their order of importance. As such, the results could be useful for general clinical practice. However, longitudinal studies and studies for each type of glaucoma are still needed.

References

1. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, Ischemic neuropathy, Papilledema, and Toxic neuropathy. Arch Ophthalmol 1982 ; 100 : 135-46.
2. Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. Am J Ophthalmol 1989 ; 107 : 453-64.
3. Tielsch JM, Katz J, Quigley HA, Miller NR, Sommer A. Intraobserver and interobserver agreement in measurement of optic disc characteristics. Ophthalmology 1988 ; 95 : 350-6.
4. Garway-Heath DF, Poinoosawmy D, Wollstein G, Viswanathan A, Kamal D, Fontana L, et al. Inter- and intraobserver variation in the analysis of optic disc images : comparison of the Heidelberg retina tomograph and computer assisted planimetry. Br J Ophthalmol 1999 ; 83 : 664-9.
5. Wollstein G, Garway-Heath DF, Fontana L, Hitchings RA. Identifying early glaucomatous changes : comparison between expert clinical assessment of optic disc photographs and confocal scanning ophthalmoscopy. Ophthalmology 2000 ; 107 : 2272-7.
6. Nicolela MT, Drance SM. Various glaucomatous optic nerve appearances : clinical correlations. Ophthalmology 1996 ; 103 : 640-9.
7. Nicolela MT, Walman BE, Buckley AR, Drance SM. Various glaucomatous optic nerve appearances. A color Doppler imaging study of retrobulbar circulation. Ophthalmology 1996 ; 103 : 1670-9.
8. Bayer A, Harasymowycz P, Henderer JD, Steinmann WG, Spaeth GL. Validity of a new disk grading scale for estimating glaucomatous damage : correlation with visual field damage. Am J Ophthalmol 2002 ; 133 : 758-63.
9. Jonas JB, Gründler AE. Correlation between mean visual field loss and morphometric optic disk variables in the open-angle glaucomas. Am J Ophthalmol 1997 ; 124 : 488-97.
10. Teesalu P, Airaksinen J, Tuulonen A. Blue-on-yellow visual field and retinal nerve fiber layer in ocular hypertension and glaucoma. Ophthalmology 1998 ; 105 : 2077-81.
11. Ishida K, Yamamoto T, Sugiyama K, Kitazawa Y. Disk hemorrhage is a significantly negative prognostic factor in normal-tension glaucoma. Am J Ophthalmol 2000 ; 129 : 707-14.
12. Sato Y, Tomita G, Onda E, Goto Y, Oguri A, Kitazawa

Y. Association between watershed zone and visual field defect in normal tension glaucoma. Jpn J Ophthalmol 2000 ; 44 : 39–45.

13. Emdadi A, Zangwill L, Sample PA, Kono Y, Anton A, Weinreb RN. Patterns of optic disk damage in patients with early focal visual field loss. Am J Ophthalmol 1998 ; 126 : 763–71.
14. Kono Y, Zangwill L, Sample PA, Jonas JB, Emdadi A, Gupta N et al. Relationship between parapapillary atrophy and visual field abnormality in primary open-angle glaucoma. Am J Ophthalmol 1999 ; 127 : 674–80.
15. Vihanninjoki K, Teesalu P, Burk ROW, Läärä E, Tuulonen A, Airaksinen PJ. Search for an optimal combination of structural and functional parameters for the diagnosis of glaucoma : multivariate analysis of confocal scanning laser tomograph, blue-on-yellow visual field and retinal nerve fiber layer data. Graefe's Arch Clin Exp Ophthalmol 2000 ; 238 : 477–81.
16. Miglior S, Casula M, Guareschi M, Marchetti I, Iester M, Orzalesi N. Clinical ability of Heidelberg Retinal Tomograph examination to detect glaucomatous visual field changes. Ophthalmology 2001 ; 108 : 1621–7.
17. Park KH, Park SJ, Lee YJ, Kim JY, Caprioli J. Ability of peripapillary atrophy parameters to differentiate normal-tension glaucoma from glaucomalike disk. J Glaucoma 2001 ; 10 : 95–101.
18. Bowd C, Zangwill LM, Berry CC, Blumenthal EZ, Vasile C, Sanchez-Galeana C, et al. Detecting early glaucoma by assessment of retinal nerve fiber layer thickness and visual function. Invest Ophthalmol Vis Sci 2001 ; 42 : 1993–2003.
19. Funaki S, Shirakashi M, Yaoeda K, Abe H, Kunimatsu S, Suzuki Y, et al. Specificity and sensitivity of glaucoma detection in the Japanese population using scanning laser polarimetry. Br J Ophthalmol 2002 ; 86 : 70–4.
20. Johnson CA, Samuels SJ. Screening for glaucomatous visual field loss with frequency-doubling perimetry. Invest Ophthalmol Vis Sci 1997 ; 38 : 413–25.
21. Anderson DR, Patella VM. Automated static perimetry. St Louis : Mosby ; 1992. p. 152–3.
22. Breiman L, Friedman JH, Olshen RA, Stone CJ. Classification and regression trees. Florida : Chapman & Hall/CRC Press ; 1984. p. 18–202.
23. Johnson CA, Sample PA, Cioffi GA, Liebmann JR, Weinreb RN. Structure and function evaluation (SAFE) : I. Criteria for glaucomatous visual field loss using standard automated perimetry (SAP) and short wavelength automated perimetry (SWAP). Am J Ophthalmol 2002 ; 134 : 177–85.
24. Sponsel WE, Arango S, Trigo Y, Mensah J. Clinical classification of glaucomatous visual field loss by frequency doubling perimetry. Am J Ophthalmol 1998 ; 125 : 830–6.
25. Nicolela MT, Drance SM, Broadway DC, Chauhan BC, McCormick TA, LeBlanc RP. Agreement among clinicians in the recognition of patterns of optic disk damage in glaucoma. Am J Ophthalmol 2001 ; 132 : 836–44.
26. Goldman L, Cook EF, Brand DA, Lee TH, Rouan GW, Weisberg MC, et al. A computer protocol to predict myocardial infarction in emergency department patients with chest pain. N Engl J Med 1988 ; 318 : 797–803.
27. Schmoor C, Ulm K, Schumacher M. Comparison of the cox model the regression tree procedure in analyzing a randomized clinical trial. Stat Med 1993 ; 12 : 2351–66.