Quantification of Retinal Nerve Fiber Defects in Glaucoma: Three-Dimensional Analysis by Heidelberg Retina Tomograph

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Purpose: To describe a new method of quantifying retinal nerve fiber layer defects (NFLD) in glaucomatous eyes using the Heidelberg Retina Tomograph (HRT).

Methods: Mean tomographic images including the optic disc and peripapillary area were constructed using HRT. An image field of 15º × 15º or 20º × 20º was used for the NFLD analysis. Data on the nerve fiber layer thickness was collected and further analyzed circumferentially across the NFLD at a position 500 μm away from the optic disc margin. We studied 31 patients with early to moderate open-angle glaucoma, ie, with visual field defects appearing earlier than stage 3 of the modified Aulhorn-Greve classification. We determined the width (W), maximum depth (D), and cross-sectional area of the NFLD (A), and we identified correlations between these parameters and the visual field indices from Humphrey Visual Field tests, mean deviation (MD) and corrected pattern standard deviation (CPSD).

Results: NFLD parameters could be obtained from 20 of 31 eyes (65%). There was a statistically significant correlation between the D and A parameters, and between these parameters and the maximum depression threshold in the corresponding visual field. No significant correlation was found between the NFLD parameters, the global visual field indices (MD, CPSD) and the mean value of the total deviation (TD) in the corresponding hemifield visual field.

Conclusions: A cross-sectional NFLD image can be obtained using HRT. Among the three NFLD parameters, maximum depth (D), and area under the surface (A) correlated well with the visual field threshold. **Jpn J Ophthalmol 2003;47:347–350** © 2003 Japanese Ophthalmological Society

Key Words: Glaucoma, Heidelberg retina tomograph, nerve fiber layer defect, three-dimensional parameters, visual field.

Introduction

It is well known that in cases of glaucoma approximately 20%–40% of the axons in the optic nerve have already been lost by the time irreversible visual field losses are detected by an automatic light threshold perimeter.[1] Morphometric changes in the optic disc and nerve fiber layer (NFL) complex usually precede glaucomatous visual field loss.[2,3]

Therefore, we should carefully observe and monitor changes in the optic disc and NFL in the diagnosis and follow-up of glaucoma.

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The NFL has traditionally been assessed using photographs taken with red-free light having a wavelength of approximately 500 nm.[4–7] Recently, the scanning laser ophthalmoscope (SLO, Rodenstock, Munich, Germany) has been employed because of its high quality images. Several investigators have attempted quantitative or semiquantitative evaluation of a nerve fiber layer defect (NFLD)[8–10] using the new imaging technology.

The Heidelberg Retina Tomograph (HRT, Heidelberg Engineering GmbH, Heidelberg, Germany) obtains layer-by-layer or topographic imaging within the optic nerve head and peripapillary NFL. This makes three-dimensional analysis of the NFL a theoretical possibility.

Burk et al[9] utilized HRT to investigate the relationship between the depth of the NFLD, or the depression of the retinal surface, and the development of a scotoma. However, they did not mention a correlation between

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NFLD parameters and the visual field indices. Thus, there are still no generally accepted methods for these analyses.

In the present study, we investigated the efficacy of a new quantification method for the NFL using HRT.

Methods

The study subjects consisted of patients with open-angle glaucoma who met the following criteria: normal open angle, glaucomatous optic nerve head change determined by direct ophthalmoscope, wedge-shaped NFLD detected in only the upper or the lower hemifield determined by fundus observation using a red-free photograph or SLO, reliable glaucomatous visual field loss earlier than stage 3 of Aulhorn-Greve's classification with the Full Threshold, Central 30-2 program of the Humphrey Field Analyzer 630 (Carl Zeiss-Humphrey Systems, Dublin, CA, USA), and no history of other ocular or intracranial diseases affecting the optic disc or visual field.

Twenty-seven patients (31eyes) with open-angle glaucoma were selected from our database. These patients consisted of 11 men and 16 women. Of the 27 patients, 23 patients (26 eyes) had normal-tension glaucoma and 4 patients (5 eyes) had primary open-angle glaucoma. All conditions were diagnosed and followed at the Glaucoma Clinic of Gifu University Hospital.

The tenets of the Declaration of Helsinki were followed in all cases, and informed consent was obtained from all patients.

The mean values (±SD) of the mean deviation (MD) and the corrected pattern standard deviation (CPSD) of the Central 30-2 program of the Humphrey Field Analyzer were—4.56 ± 4.12 dB and 8.19 ± 2.87 dB, respectively.

All subjects were examined by the same examiner (HU) using an HRT. Three consecutive HRT images around the optic disc including the peripapillary area in a field of 15º × 15º or 20º × 20º were used to obtain the mean topographic images. The mean topographic images having less than 30 μm of mean standard deviation of pixel were used for further analysis. Data on the nerve fiber layer thickness were collected and analyzed circumferentially across the NFLD at a position 500 μm away from the optic disc margin. We also analyzed the bridging of healthy NFL for a width of at least 200 μm at both edges. The NFLD edges (a, b) were qualitatively determined by one examiner (KM) viewing the monitor. Using this line, the height of the retinal surface, ie, the internal limiting membrane was continuously measured (Figure 1). The point coordinates (X, Y, and Z) obtained from the HRT images were input into an EXCEL spreadsheet (Microsoft Excel 2000) to develop the cross-sectional image of the NFLD (Figure 2).

If any blood vessels crossing the NFLD were detected, we skipped the points of the vessel surface from end to end of the vessels to normalize the NFL surface. We defined the new parameters of the NFLD as follows: (1) the width parameter (W) which is defined as the width of an NFLD at a position 500 μm from the optic disc margin; (2) the maximum depth parameter (D) which corresponds to the maximum depth in an NFLD cross-sectional image; and (3) the cross-sectional area parameter (A) which refers to the NFLD area under the relatively healthy retinal surface. To obtain measurement reproducibility, we measured five randomly chosen eyes and their NFLD parameters (W, D, A) three times on the same day using a single examiner (KM).

We used Spearman's rank correlation test to identify the correlation between each of the NFLD parameters (W, D, A) and (1) each of the visual field indices (MD, CPSD) in the Humphrey Field Analyzer Central 30-2, and (2) the mean and maximum value of the TD in the hemifield site corresponding to the NFLD site.

A P value of less than .05 was considered to indicate a statistically significant correlation.

Results

A cross-sectional image of the wedge-shaped NFLD was obtained in 20 of 31 eyes (65%). The remaining 11 eyes (35%) showed a sawtooth-shaped NFLD and the three parameters could not be obtained (Figure 3). The mean (±SD) coefficients of variation of W were 3.63 (±1.7)% (range: 1.37%–5.90%), respectively. The mean (±SD) coefficients of variation of D were 4.14 (±0.24)% (range: 1.74%–7.63%), respectively. The mean (±SD) coefficients of variation of A were 4.96 (±0.14)% (range: 3.57%–7.40%), respectively.

There was a statistically significant correlation between two parameters (D, A), and the maximum depression threshold in the corresponding hemisphere visual field site ($r = .603$, $P = .0086$; $r = .548$, $P = .02$, respectively) (Figure 4). There were no statistically significant correlations between the three parameters (W, D, A) and the visual field indices (MD, CPSD) nor in the mean TD in the hemisphere visual field site corresponding to the NFLD site.

Discussion

Conventionally, the NFLD has been evaluated according to its brightness, shade, and texture by means of red-free light fundus photographs.[4–7] Recently, SLO has

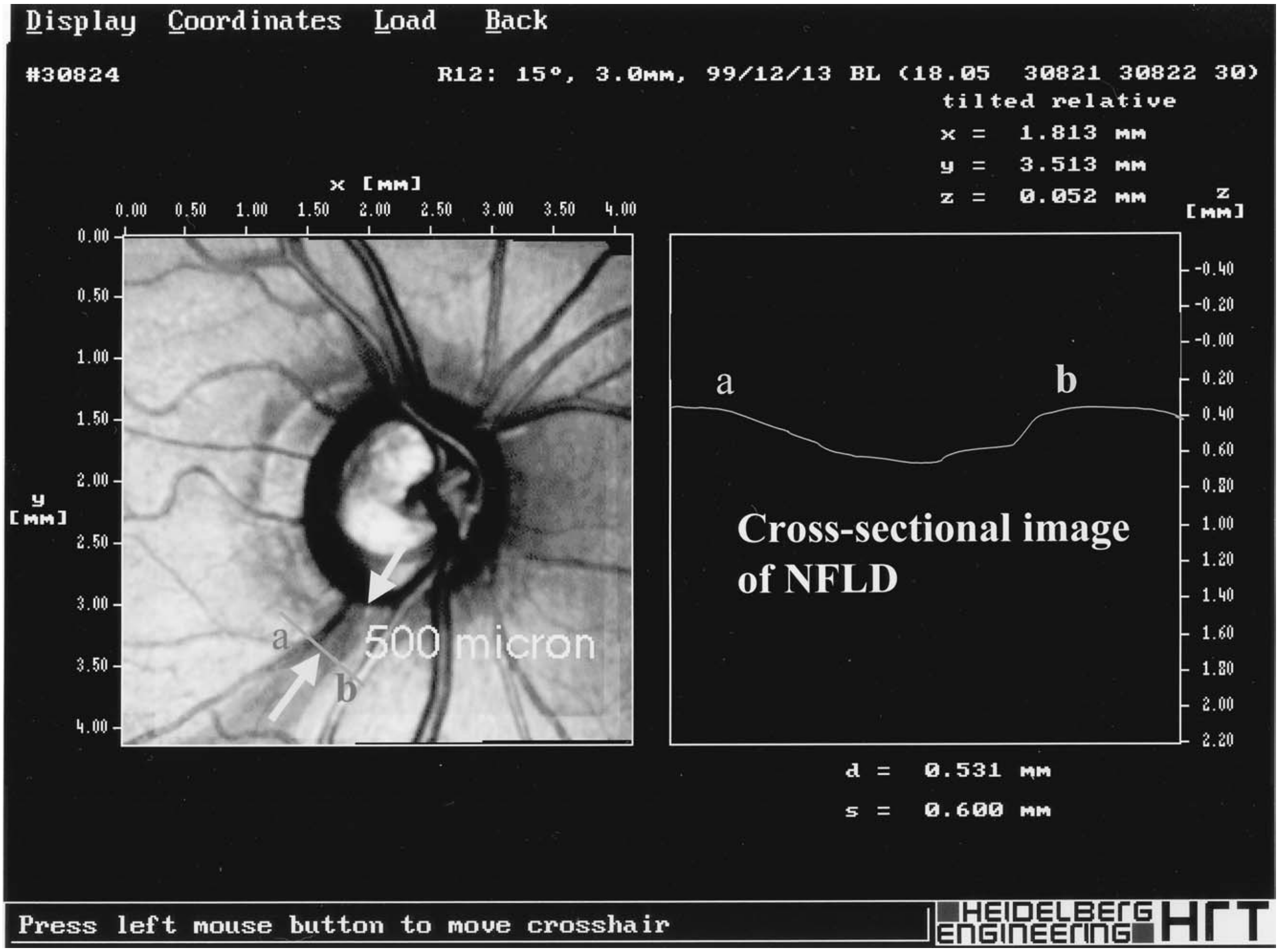

Figure 1. Sample images obtained in nerve fiber layer of glaucoma patients by Heidelberg Retina Tomography imaging to quantify nerve fiber layer defects (NFLD). The NFLD cross-sectional image was obtained by continuous measurement utilizing a straight line drawn to connect two marginal points, a and b, of the particular NFLD 500 μm.

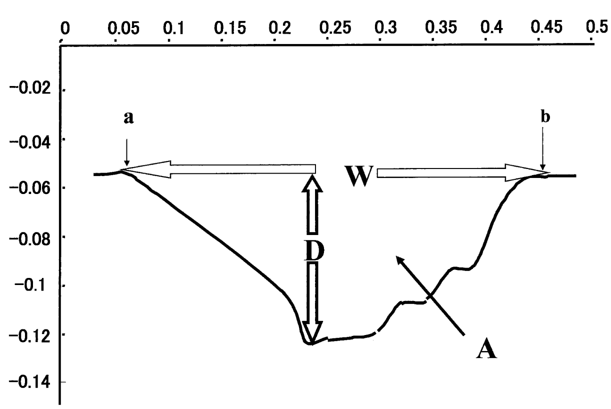

Figure 2. NFLD cross-sectional image from case 1 (expansion by EXCEL). The NFLD cross-sectional image and the parameters (width, W; maximum depth, D; and cross-sectional area, A) obtained by input of the individual measuring axes obtained from Figure 1 into an EXCEL program (Ver. 5.0, Microsoft).

been employed to evaluate the NFLD in glaucoma because of its high-quality images.

Quigley et al[8] proposed a method of grading an NFLD based on the retinal nerve fiber surface brightness and

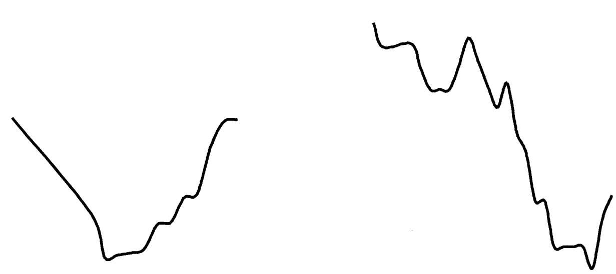

Figure 3. Two types of NFLD cross-sectional images. Conical cross-sectional images (left) were obtained from 20 of 31 eyes (65%), and saw-toothed cross-sectional images (right) were obtained from the remaining 11 eyes (35%).

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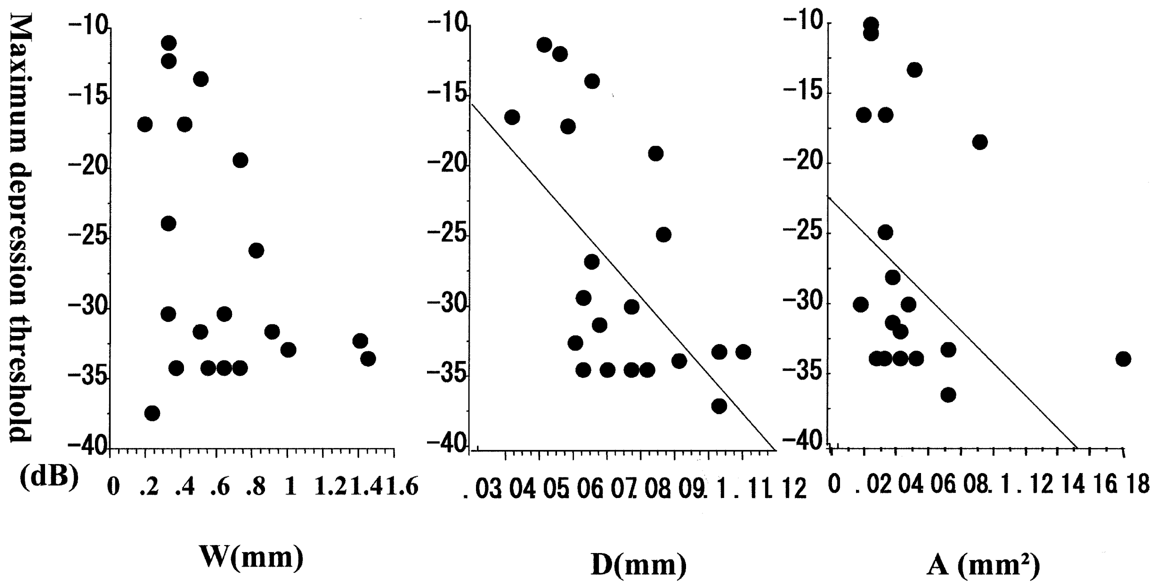

Figure 4. Correlation between the three parameters, and between these parameters and the maximum depression threshold in the corresponding visual field. Statistically significant differences were found for the D and A parameters (r = .603, P = .0086, r = .548, P = .02, respectively).

texture using red-free light fundus photographs. Uchida et al[10] studied the relationship between the central visual field defects and any of the following NFLD parameters. They suggested that these quantitative NFLD parameters may be helpful for evaluating parafoveal visual function in glaucomatous eyes. While these studies attempted to develop an NFLD grading system either semi-quantitatively or quantitatively, they did not include the three-dimensional NFLD parameters, such as depth and cross-sectional area.

HRT, a recently developed confocal scanning laser ophthalmoscope, makes possible a three-dimensional analysis of the optic nerve head and retinal surface, even for a wedge-shaped NFLD. We applied this technology to evaluate three-dimensional NFLD parameters such as its depth and cross-sectional area.

In the present study, using HRT, we constructed a cross-sectional image of an NFLD and found that the newly defined D and A parameters correlated well with the maximum depression threshold in the corresponding hemifield. Reproducibility of this NFLD measurement was excellent (>5%). Our findings suggest that the deeper the NFLD, the greater the depression threshold of the visual field. These new cross-sectional parameters (D, A) may better reflect the visual field threshold than the conventional parameter (W).

However, this determination will require a long-term follow-up study using the methods defined here. The present study focused on glaucomatous eyes found by static perimeter to have both an NFLD and a visual field loss.

Future studies should include glaucomatous eyes having an NFLD without visual field loss to determine whether, in such cases, the NFLD parameters change prior to the deterioration of the visual field.

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