Relationship between Retinal Nerve Fiber Layer Thickness and Early Glaucomatous Changes in the Adolescents

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Purpose: To evaluate of usefulness of retinal nerve fiber layer thickness as measured by optical coherence tomography (OCT) in children and young adolescents in the diagnosis of glaucoma, ocular hypertension, and glaucoma suspect.

Methods: In total, 234 patients aged <18 years were included in this study (21 eyes with glaucoma, 179 suspected glaucoma eyes, and 34 eyes with ocular hypertension). All patients underwent OCT to measure the retinal nerve fiber layer thickness, Humphrey visual field testing if possible, and other ocular examinations. Based on the OCT results, we classified the eyes into 4 o’clock-hour and 12 o’clock-hour sectors and compared these data with other clinical ocular findings.

Results: The retinal nerve fiber layer thickness as measured by OCT was correlated with the vertical cup-disc ratio. An OCT 330° (Sup) value of <140 µm or an average OCT value of <105 µm is useful for the prediction of a vertical cup-disc ratio of >0.6.

Conclusions: A higher vertical cup-disc ratio is associated with a lower retinal nerve fiber layer thickness, not only with back-bowing of the lamina cribrosa or normal variation. An OCT 330° (Sup) value of <140 µm or average OCT value of <105 µm is a useful index with which to predict early glaucomatous changes in pediatric and young adolescent patients.

Key words: Childhood glaucoma, Glaucoma suspect, Nerve fiber layer thickness, Ocular hypertension, Optical coherence tomography

Introduction

Detection of glaucomatous damage can be problematic, particularly in juveniles. Diagnosis is typically achieved through observation of the optic nerve head and retinal nerve fiber layer (RNFL) and measurement of the visual function with perimetry. These methods are subjective examinations, however, and cannot provide a reliable early diagnosis. Defects in the RNFL may be an early sign of glaucoma, preceding optic disc and visual field changes. Optical coherence tomography (OCT), a new noninvasive technology allowing for cross-sectional imaging of the eye, was recently reported to offer the possibility of assessing the RNFL thickness with good reproducibility.

OCT is an imaging technology that was developed to detect retinal and RNFL damage. In OCT, the RNFL thickness is most often measured using peripapillary scanning around the optic disc. The Stratus OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) has the ability to quantify the RNFL thickness with a resolution of 8 to 10 µm and can thus potentially diagnose glaucoma much earlier. A number of recent studies have reported that OCT can detect glaucomatous damage with moderate to reasonably high sensitivity and specificity. In these studies, the
sensitivity/specificity ranged from 76%/81% to 91%/100%, respectively.6-8

The diagnosis of glaucoma in children and young adults has been very difficult for clinical ophthalmologists because visual field examination in young patients is relatively unreliable and there is currently no normative OCT database for patients aged <18 years. Considering this background, we attempted to identify a correlation between the clinical outcomes of these patients and the thickness of the RNFL and to determine whether OCT is a useful diagnostic tool for young patients with glaucoma.

Materials and Methods

The study population comprised 234 patients aged <18 years who visited the ophthalmologic clinic. One eye was randomly chosen for each patient. Informed consent was obtained from all patients before their participation. All study procedures adhered to the tenets of the Declaration of Helsinki, and the study protocol was approved by the Institutional Board of Research Associates of the Incheon St. Mary’s hospital, Catholic University of Korea.

The inclusion criteria were a clear lens, normal retina, and open angle state. The exclusion criteria were myopia of greater than -8 diopters, optic disc nerve disease other than glaucoma, and a history of neuro-ophthalmologic disease.

This study included 234 eyes of 132 boys and 102 girls (age range, 2-18 years; mean age ± standard deviation, 13.50 ± 3.81 years). The patients’ diagnoses were glaucoma in 21 eyes, suspected glaucoma in 179 eyes, and ocular hypertension in 34 eyes. All patients underwent a complete ophthalmologic examination, including a medical, ocular, and family history; visual acuity testing with refraction; Humphrey field analyzer testing (Zeiss Humphrey Systems, Dublin, CA, USA) with 24-2 standard achromatic perimetry if possible; intracocular pressure (IOP); dilated slit-lamp stereo biomicroscopy; direct and indirect ophthalmoscopy; and stereoscopic optic nerve head photography.

Test eyes were classified as glaucomatous based on the following criteria: 1) the diagnosis of glaucoma was based on a reliable field defect in the Humphrey visual field examination; 2) suspected glaucoma was defined as a vertical cup/disc ratio of >0.6 in the dilated slit-lamp examination with no other abnormal ocular findings; and 3) ocular hypertension was defined as an IOP of >21 mmHg and no other abnormal ocular findings.

Stratus OCT

OCT measures the peripapillary RNFL thickness according to the difference between the temporal delay of backscattered light from the RNFL and a reference beam. The RNFL is differentiated from other retinal layers using an edge-detection algorithm. The RNFL thickness is defined as the number of pixels between the anterior and posterior edges of the RNFL. Each resulting image constitutes the RNFL thickness measurements (μm) at 100 points along a 360° circular ring around the optic disk. For this study, three acceptable-quality circular scans of 3.4 mm diameter centered on the optic disk were obtained for each test eye. This approximate scan diameter was found to be optimal for RNFL analysis in a prototype instrument. The RNFL thickness is presented for each of the four quadrants (superior, inferior, nasal, and temporal) in clock h (12 sectors) and as the average RNFL thickness.

Data Analysis and Statistics

The Stratus OCT software (version A4.0.3, Carl Zeiss Meditec Inc.) calculates several parameters that are summarized in the Stratus OCT RNFL Thickness Average Analysis Report; these parameters are referred to as summary report parameters in this paper. They include full circle, quadrant, and clock-hour RNFL thickness and eight “new” parameters introduced with the Stratus OCT, namely the Imax/Smax, Smax/Imax, Smax/Tavg, Imax/Tavg, and Smax/Navg ratios; the Max-Min difference; the Smax; and the Imax.

The following analytic steps were taken: (1) correlations between the values of all parameters and the clinical characteristics (CD) ratio (vertical [v] and horizontal [h], IOP, and age) were calculated; (2) significantly different values of parameters among patients with glaucoma, suspected glaucoma, and ocular hypertension were identified (in one-
way ANOVA, \( p < 0.05 \) indicated a statistically significant difference; (3) significantly different values of parameters between patients with a CD (v) ratio of >0.6 or IOP of >21 mmHg and other patients were identified (between a CD [v] ratio of >0.6 and an IOP of <21 mmHg and other patients, and between a CD ratio of >0.6 and an IOP of >21 mmHg and other patients; in the Mann-Whitney \( U \) test, \( p < 0.05 \) indicated a statistically significant difference); and (4) receiver operating characteristic (ROC) curves were created using the values collected in steps (1), (2), and (3), and a new discriminant score was obtained by discriminant analysis. Statistical analyses were carried out using SPSS for Windows, version 12 (IBM Corp., Armonk, NY, USA).

### Table 1. Patients characteristics and clinical findings

|               | Glaucoma | Glaucoma suspect | Ocular hypertension |
|---------------|----------|------------------|---------------------|
| Eyes          | 21       | 179              | 34                  |
| Age (years)   | 10.23 ± 2.85 | 13.70 ± 3.42     | 11.35 ± 4.21        |
| Gender (f/m)  | 10/11    | 75/104           | 12/23               |
| Side (r/l)    | 13/8     | 73/106           | 15/19               |
| Refractive error (D) | -4.52 ± 2.30 | -2.25 ± 3.2    | -1.82 ± 1.93        |

Values are presented as mean ± standard deviation or number. f/m = female/male; r/l = right/left; D = diopter.

### Table 2. Correlation between RNFL thickness and CD (v)/(h) ratio IOP or Age

|               | CD (v) ratio | CD (h) ratio | IOP | Age |
|---------------|--------------|--------------|-----|-----|
| OCT-0°        | -0.1915      | 0.008        | -0.0697 | 0.644 | 0.0532 | 0.451 |
| OCT-30°       | -0.1203      | 0.093        | -0.1094 | 0.998 | 0.0427 | 0.545 |
| OCT-60°       | -0.0002      | 0.978        | -0.0758 | 0.828 | -0.0112 | 0.874 |
| OCT-90°       | -0.0975      | 0.372        | 0.0221 | 0.454 | 0.1226 | 0.081 |
| OCT-120°      | -0.2234      | 0.003        | -0.0135 | 0.487 | 0.2442 | 0.000 |
| OCT-150°      | -0.0692      | 0.296        | -0.0895 | 0.977 | -0.0202 | 0.775 |
| OCT-180°      | -0.0453      | 0.389        | -0.0650 | 0.501 | 0.1021 | 0.147 |
| OCT-210°      | -0.2494      | 0.002        | -0.1423 | 0.482 | 0.1472 | 0.036 |
| OCT-240°      | -0.2086      | 0.003        | -0.0982 | 0.270 | 0.1503 | 0.032 |
| OCT-270°      | -0.1628      | 0.022        | -0.0956 | 0.296 | 0.1833 | 0.009 |
| OCT-300°      | -0.1765      | 0.028        | -0.1538 | 0.170 | 0.0988 | 0.161 |
| OCT-330°      | -0.3101      | 0.000        | -0.1889 | 0.274 | 0.1994 | 0.004 |
| OCT-S         | -0.2447      | 0.001        | -0.1712 | 0.504 | 0.0594 | 0.400 |
| OCT-N         | -0.0072      | 0.942        | 0.0165 | 0.270 | 0.0716 | 0.309 |
| OCT-I         | -0.2566      | 0.000        | -0.1193 | 0.858 | 0.1147 | 0.105 |
| OCT-T         | -0.1864      | 0.011        | -0.1370 | 0.118 | 0.1410 | 0.045 |
| OCT-S avg     | -0.2018      | 0.008        | -0.1876 | 0.340 | 0.0578 | 0.413 |
| OCT-I avg     | -0.2384      | 0.001        | -0.1250 | 0.907 | 0.1102 | 0.118 |
| OCT-avg       | -0.2948      | 0.000        | -0.1732 | 0.570 | 0.1339 | 0.057 |

r is correlation coefficient. RNFL = retinal nerve fiber layer; CD (v) ratio = vertical cup-disc ratio; CD (h) ratio = horizontal cup-disc ratio; IOP = intraocular pressure; S = superior; N = nasal; I = inferior; T = temporal; avg = average.

*Statistical significance was tested by Pearson’s correlation test.*
Results

Patient characteristics are shown in Table 1. In the statistical analysis of correlations between RNFL thickness and clinical characteristics (vertical CD ratio, horizontal CD ratio, IOP, and age), we found that RNFL thickness was more closely correlated with the vertical CD ratio than with the other parameters (13 of 19 parameters were statistically significant) (Table 2). In the statistical analysis of correlations between the RNFL thickness and various parameters among the glaucoma group, suspected glaucoma group, and ocular hypertension group, 12 of 19 parameters showed statistically significant correlations.

The difference in RNFL thickness was statistically significant in 14 of 19 parameters between the group with a CD (v) ratio of >0.6 or IOP of >21 mmHg and the group with other CD (v) ratio and IOP measurements (Table 3). The difference in RNFL thickness was statistically significant in 3 of 19 parameters between group with a CD (v) ratio of >0.6 and IOP of >21 mmHg and the group with other CD (v) ratio and IOP measurements (Table 4).

ROC curves were conducted with parameters such as OCT-210°, OCT-270°, OCT-330°, OCT-I, OCT-T, and OCT-avg, which were collected for statistically significant values obtained in the above-described steps (1), (2), and (3). New discriminant scores were finally obtained with OCT-330° and OCT-avg, which had the two largest areas under the ROC curves and were thought to be the best discrimination parameters.

Discriminant Analysis

The new discriminant score had a sensitivity of 80.2%, specificity of 78.4%, and cut-off value of -10.45. A cut-off value lower than -10.45 indicated a vertical CD ratio of >0.6

Table 3. The difference of RNFL thickness between group of CD (v) ratio >0.6 or IOP >21 mmHg and group of others

| Parameter | Else | CD (v) ratio >0.6 or IOP >21 mmHg | p-value*
|---|---|---|---
| OCT-0° | 132.87 ± 30.13 | 126.06 ± 33.96 | 0.1731
| OCT-30° | 119.17 ± 26.22 | 112.37 ± 31.79 | 0.1389
| OCT-60° | 86.16 ± 21.77 | 81.69 ± 25.48 | 0.2283
| OCT-90° | 61.11 ± 16.35 | 55.61 ± 16.04 | 0.0257
| OCT-120° | 83.87 ± 24.40 | 72.34 ± 21.69 | 0.0099
| OCT-150° | 104.17 ± 26.54 | 101.50 ± 25.37 | 0.4941
| OCT-180° | 141.56 ± 26.60 | 138.94 ± 29.73 | 0.5494
| OCT-210° | 159.71 ± 25.05 | 148.94 ± 29.60 | 0.0128
| OCT-240° | 95.71 ± 27.30 | 87.57 ± 21.76 | 0.0394
| OCT-270° | 73.81 ± 21.46 | 64.83 ± 18.90 | 0.0030
| OCT-300° | 98.27 ± 23.53 | 88.55 ± 22.25 | 0.0052
| OCT-330° | 149.87 ± 22.43 | 136.40 ± 30.07 | 0.0005
| OCT-S | 134.63 ± 21.08 | 123.41 ± 28.01 | 0.0019
| OCT-N | 74.08 ± 16.73 | 68.18 ± 20.13 | 0.0433
| OCT-I | 137.16 ± 16.08 | 128.63 ± 23.40 | 0.0030
| OCT-T | 89.78 ± 20.11 | 80.56 ± 20.01 | 0.0028
| OCT-S avg | 134.68 ± 21.09 | 123.12 ± 28.99 | 0.0017
| OCT-I avg | 137.16 ± 16.08 | 128.61 ± 25.16 | 0.0041
| OCT-avg | 108.09 ± 9.99 | 100.50 ± 15.74 | <0.0001

Values are presented as mean ± standard deviation.

RNFL = retinal nerve fiber layer; CD (v) ratio = vertical cup-disc ratio; IOP = intraocular pressure; OCT = optical coherence tomography; S = superior; N = nasal; I = inferior; T = temporal; avg = average.

*Statistical significance was tested by Mann-Whitney U test.
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and it was thought to be a useful index for detection of early glaucomatous change.

Y (vertical CD ratio of ≥0.6) = age + IOP + OCT-330° + OCT-avg

New discriminant score = (-0.316 × age) + (-0.11683 × IOP) + (-0.00914 × OCT-330°) + (-0.0246 × OCT-avg)

Table 4. The difference of RNFL thickness between group of CD (v) ratio >0.6 and IOP >21 mmHg, and group of others

| Parameter   | Else                | CD (v) ratio >0.6 and IOP >21 mmHg | p-value * |
|-------------|---------------------|-----------------------------------|-----------|
| OCT-0°      | 129.40 ± 31.12      | 104.60 ± 54.61                    | 0.1871    |
| OCT-30°     | 115.73 ± 28.95      | 90.40 ± 44.90                     | 0.1099    |
| OCT-60°     | 83.74 ± 24.38       | 70.20 ± 22.73                     | 0.0874    |
| OCT-90°     | 57.75 ± 16.06       | 49.00 ± 19.39                     | 0.0981    |
| OCT-120°    | 75.94 ± 22.44       | 75.50 ± 35.60                     | 0.9701    |
| OCT-150°    | 103.26 ± 24.47      | 84.30 ± 40.93                     | 0.1794    |
| OCT-180°    | 140.47 ± 26.99      | 125.80 ± 52.79                    | 0.4048    |
| OCT-210°    | 153.66 ± 6.62       | 125.70 ± 49.62                    | 0.1098    |
| OCT-240°    | 90.44 ± 22.99       | 83.50 ± 37.98                     | 0.5805    |
| OCT-270°    | 68.00 ± 20.15       | 60.20 ± 18.92                     | 0.2327    |
| OCT-300°    | 92.71 ± 22.22       | 69.50 ± 28.60                     | 0.0017    |
| OCT-330°    | 142.45 ± 26.41      | 104.60 ± 43.71                    | 0.0231    |
| OCT-S       | 128.25 ± 24.74      | 100.70 ± 43.89                    | 0.0795    |
| OCT-N       | 69.96 ± 18.53       | 70.70 ± 32.19                     | 0.9444    |
| OCT-I       | 132.27 ± 20.45      | 110.22 ± 35.78                    | 0.1028    |
| OCT-T       | 83.37 ± 19.57       | 74.22 ± 34.76                     | 0.4320    |
| OCT-S avg   | 128.08 ± 25.54      | 100.30 ± 44.27                    | 0.0796    |
| OCT-I avg   | 132.59 ± 21.44      | 105.70 ± 36.64                    | 0.0460    |
| OCT-avg     | 103.94 ± 13.64      | 86.91 ± 24.01                     | 0.0522    |

Values are presented as mean ± standard deviation.
RNFL = retinal nerve fiber layer; CD (v) ratio = vertical cup-disc ratio; IOP = intraocular pressure; OCT = optical coherence tomography; S = superior; N = nasal; I = inferior; T = temporal; avg = average.
*Statistical significance was tested by Mann-Whitney U test.

Discussion

Detection of glaucomatous damage can be problematic, particularly in juveniles, and is typically achieved through observation of the optic nerve head and RNFL and measurement of the visual function perimetry. These methods are subjective examinations, however, and cannot provide a reliable early diagnosis. OCT is a new and promising technology that allows for precise cross-sectional imaging of the eye. OCT is the optical analog of the ultrasound B scan, providing images with much higher resolution in both the axial and lateral dimensions. OCT scans generate one-dimensional images of the retina, from which the RNFL thickness can be directly measured. The automated computer algorithm quantitates the RNFL thickness and the entire retinal thickness as a red and strongly reflected layer at the boundary between the retina and vitreous. It shows the thickness of the superior, inferior, temporal, and nasal quadrants; the clock-hour sections; and the entire retina. The measurement technique is relatively objective and highly reproducible in pediatric and young adult patients.

Mrugacz and Bakunowicz-Lazarczyk observed a significant reduction in the mean and inferior-quadrant RNFL thickness of patients with juvenile glaucoma. In accord-
ance with Bowd et al., the mean RNFL thickness and the RNFL thicknesses in the inferior and nasal quadrants were significantly thinner in glaucomatous than in normal eyes. Ahn et al. measured the RNFL thickness in normal Korean children and adolescents with OCT, and this method was applicable to the early diagnosis of glaucoma and to the examination of its progression in both pediatric and adolescent patients with glaucoma.

The results of several clinical studies support the idea that damage to the optic nerve and RNFL can be identified before changes in the visual field. These findings are very important in the examination of children, because determination of the visual field and interpretation of the results may cause a number of problems, and the method and measurements may be more subjective and less reliable than those in older patients. Several investigations have reported that RNFL damage secondary to retinal ganglion cell damage could become an important marker of ocular function impairment and that such reductions in the RNFL thickness precedes the optic disc changes in patients with glaucoma.

In our study of children and adolescents, we found that the OCT Stratus summary report parameters yielded good diagnostic sensitivity and specificity. In previous studies, however, the inferior quadrant had important parameters associated with the glaucoma status. Our conclusion differed in that the new discriminate score contained OCT-330° and OCT-avg. In conclusion, the present results indicate that RNFL thickness as measured by OCT is a very useful tool for tracking glaucoma progression and may also be useful for pediatric screening at the population level.

Conflict of Interest Statement

The authors have declared that no conflict of interest exists.

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