The Time Course of Visual Field Recovery and Changes of Retinal Ganglion Cells after Optic Chiasmal Decompression

Chan Hee Moon,1 Sun Chul Hwang,2 Young-Hoon Ohn,1 and Tae Kwann Park1

PURPOSE. To investigate the time course of visual field recovery and changes of retinal ganglion cells (RGCs) after chiasmal decompression using standard automated perimetry (SAP), optical coherence tomography (OCT), and photopic negative response (PhNR).

METHODS. Nineteen patients undergoing chiasmal decompression surgery were prospectively assessed before and 1 and 3 months after surgery. The same examinations were conducted in nine patients at 6 months after surgery. Mean deviation and temporal visual field sensitivity (1/Lambert) of SAP, retinal nerve fiber layer (RNFL) thickness, and ganglion cell complex (GCC) area measured by OCT and PhNR/b-wave ratio were analyzed. Preoperative measurements were compared with those of 20 eyes of normal controls. Postoperative measurements were compared with preoperative data. The relationships among SAP, OCT, and PhNR measurements throughout the observation periods were evaluated by linear and logarithmic regressions.

RESULTS. Before surgery, all parameters in patients were significantly worse than those in normal controls. After surgery, the visual field was significantly improved, but RNFL thickness and GCC area were significantly reduced for 3 months. The PhNR/b-wave ratio was also reduced, but not significantly. Six months after surgery, average RNFL thickness, GCC area, and PhNR/b-wave ratio showed significant improvements by 2.82%, 2.66%, and 8.72%, respectively, than those at 3 months. Visual fields were significantly correlated with RNFL thickness, GCC area, and PhNR/b-wave ratio.

CONCLUSIONS. Visual field recovery and changes of RGCs after chiasmal decompression have similar aspects and are significantly correlated. However, prolonged retrograde degeneration progressed for some period, even after surgical decompression and visual field recovery preceded demonstrable retinal regeneration. (Invest Ophthalmol Vis Sci. 2011;52:7966–7973) DOI:10.1167/iovs.11-7450

Compressive lesions at the optic chiasm can produce losses in visual acuity (VA), defects in the visual field (VF), and degraded color perceptions in both eyes.1–3 Visual dysfunctions are a consequence of damage to retinal ganglion cells (RGCs) and their axons.

Potential mechanisms of axonal injury from a compressive chiasmal lesion include direct disruption of conduction along the axon, impairment of anterograde and retrograde axoplasmic flow, and demyelination with impaired signal conduction.4 RGCs also die as a result of axonal injury, a phenomenon referred to as retrograde degeneration.5,6 Because the degree of visual dysfunction and recovery after surgical decompression is dependent on the amount of injury and recovery of RGCs, it is valuable to know the structural and functional changes of RGCs before and after the surgery involving their time course from both objective and quantitative perspectives.

Visual evoked potential,7,8 pattern electroretinogram (PERG),9,10 and photopic negative response (PhNR)11–14 are used to evaluate functional damage to RGCs. Optical coherence tomography (OCT) is used in the assessment of structural damage to retinal nerve fibers and RGCs by quantifying the thickness of the RNFL and the whole retinal thickness.15–21 Previous reports have also investigated a variety of candidate measures, using OCT, PERG, and PhNR. However, most of these studies either have been cross-sectional studies or have been focused on locating prognostic factors to assess the relationship between the degree of measures before surgery and the recovery of visual function after surgery.

In this prospective study, we investigated the time course and relationship of visual field recovery and changes in retinal structure and function after chiasmal decompression using standard automated perimetry (SAP), OCT, and PhNR.

METHODS

Subjects

Twenty-three consecutive patients diagnosed with chiasmal compression syndrome were prospectively recruited from the Ophthalmology and Neurosurgery Departments in our institution, between January 1, 2010 and March 25, 2011. The research adhered to the tenets of the Declaration of Helsinki. The institutional review board had approved the research and informed consent had been obtained.

Inclusion criteria were chiasmal compressive lesion confirmed by magnetic resonance imaging (MRI), with preoperative VF impairment as determined by SAP using a visual field analyzer (Humphrey Field Analyzer II [HFAII]; Carl Zeiss Meditec, Dublin, CA), and transphenoidal or transcranial surgery. Only one eye (the one with the lesser VF defect) of each patient was selected for analysis.

In the preoperative assessment, all patients underwent complete ophthalmic examinations including VA, intraocular pressure (IOP), refraction, slit-lamp biomicroscopy, gonioscopy, dilated stereoscopic fundus examination, SAP, OCT, and PhNR. At 1 and 3 months after surgery, repeated VA, IOP, slit-lamp biomicroscopy, fundus examination, SAP, OCT, and PhNR measurements were conducted. Additionally, nine patients were subjected to extended assessment and identical examinations were conducted at 6 months after surgery.

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Exclusion criteria were as follows: any previous treatment, including radiotherapy or medical treatment; any anterior segment, retinal, posterior segment, or optic nerve disease other than compressive optic neuropathy; a history of diabetes or any other systemic illness that might affect the retina and optic nerve; an unreliable VF testing >20% false positive, false negative, or fixation loss; a spherical refractive error outside the range of ±5D; and postoperative complications, including intracranial hemorrhage, cerebral edema, and further surgery for the treatment of complications or tumor recurrence.

Nineteen patients met the inclusion criteria and 19 eyes were included in the analysis. Four patients did not meet the inclusion criteria because of incomplete resection of tumor (one patient), intracranial hemorrhage after surgery (one patient), and not completing the follow-up protocol for the postoperative assessment (two patients).

### Brain Imaging

MRI was performed before and 3 months after surgery. Compression of the anterior visual pathway was confirmed before surgery. Tumor size was evaluated by measuring the longest width, length, and height and multiplying them. Compression relief was confirmed on follow-up MRI at 3 months after surgery, and the residual tumor size was also evaluated.

### Automated Perimetry

Automated perimetry was conducted using the 30-2 central test point patterns of the Swedish interactive threshold algorithm visual field analyzer (HFA-II; Carl Zeiss Meditec), with a size III stimulus (Goldmann perimetry) on a 31.5-apostilb background. According to the field defects, patients were graded into the following four subgroups: Grade 1, quadrantanopsia; Grade 2, partial hemianopsia; Grade 3, complete hemianopsia; Grade 4, three quadrantanopsia or worse. Mean grades of visual field defects before and after surgery were compared. The mean deviation (MD) and pattern SD (PSD) were analyzed. Additionally, because visual field loss in chiasmal compression is usually more significant in the temporal field, the average visual sensitivity of the temporal hemifield was calculated at the 1/Lambert scale. Since visual field sensitivity was recorded for each point using the decibel (dB) (10 log10/Lambert), 1/Lambert scale at each test location was calculated by dividing the decibel unit by 10 and then unlogging it.

### Optical Coherence Tomography

OCT imaging was conducted after pupil dilation using spectral domain (SD)-OCT (Cirrus software version 4.5.1.11; Carl Zeiss Meditec). RNFL thickness measurements were obtained using an optic disc cube protocol, consisting of 200 x 200 scans. Peripapillary RNFL thickness of each quadrant (superior, temporal, inferior, and nasal) and their average values were analyzed.

GCC was defined as the combination of nerve fiber, ganglion cell, and inner plexiform layers. Vertical and horizontal cross-sectional images of the macula involving the foveola were obtained using a macular cube protocol, consisting of 512 x 128 scans. The GCC area was measured using the polygonal selection tool software (Image) 1.43u, developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html). Measurements in vertical scan (vertical value), horizontal scan (horizontal value), and average value were analyzed.

### Photopic Negative Response

Before the electroretinogram (ERG) recordings, the pupils were confirmed to be maximally dilated to approximately 8 mm in diameter after the topical application of 1% tropicamide and 2.5% phenylephrine hydrochloride. Subjects underwent light adaptation by means of a white background light of 31.9 cd/m2 for 10 minutes. After corneal anesthesia with 0.5% proparacaine (Alcaine; Alcon Laboratories, Sinking Spring, PA), a bipolar contact lens electrode (Burian-Allen ERG electrode; Hansen Ophthalmic Laboratories, Iowa City, IA) was inserted into the conjunctival sac. The ground electrode was placed on the earlobe. Full-field light stimulation was then produced, using a light dome (Ganzfeld Dome; Biomedica Mangoni, Snc. Pisà, Italy). A commercially available photostimulator (PS22, Grass-Telefactor; Astro-Med, Inc., West Warwick, RI) was used to generate light stimuli, and a white stimulus was applied at an intensity of 2.4 x 10^-6 cd · s/m² under a 31.9 cd/m² white background illumination. ERG was recorded using a recording device (UTAS-E3000; LKC Technologies, Inc., Gaithersburg, MD). The duration of the stimulation was limited to <5 ms. The PhNR amplitude was measured from the baseline to the negative trough between the cone b-wave and the i-wave. To reduce the variations of the PhNR amplitude among individuals, the ratio of the PhNR amplitude to the b-wave (PhNR/b-wave ratio) was evaluated.

### Statistical Analysis

A Mann–Whitney U test was conducted to compare SAP, OCT, and PhNR measurements between normal controls and patients. Wilcoxon signed-ranks test was conducted to compare changes in measurements of SAP, OCT, and PhNR before and 1 and 3 months after surgery. Linear regression analysis was conducted to determine the relationship between RNFL thickness and the GCC area and PhNR, all of which reflect the degree of injury to RGCs. Combining all the data obtained before and after surgery, linear and logarithmic regression analyses were conducted to evaluate the relationship between RNFL thickness, GCC area, PhNR/b-wave ratio, and SAP throughout the observation period. MD and temporal visual sensitivity (1/Lambert) were treated as dependent variables and the others were treated as independent variables in all regressions. The relationship between decibel light sensitivity and ganglion cell number is curvilinear and can be explained by a logarithmic regression, which was conducted in addition to the linear regression.22–24 The relationship between temporal visual sensitivity (1/Lambert) and measurements of OCT and PhNR was assessed by linear regression analysis.

Statistical analysis was conducted using analytical software (SPSS version 15.0 for Windows; SPSS Inc., Chicago, IL). All tests were two-tailed and P < 0.05 was considered statistically significant.

### RESULTS

#### General Characteristics

The average age of patients was 53.52 ± 10.66 years, with 7 males and 12 females. The patients had a diagnosis of pituitary adenoma (16 patients), cranioopharyngioma (2 patients), and meningioma (1 patient). A transsphenoidal approach (TSA) was used in 16 patients and a transcranial approach (TCA) was applied in 3 patients. The average tumor volume was 15.21 ± 5.76 cm³ before and 1.28 ± 2.44 cm³ after surgery. Complete or nearly complete decompression of the anterior visual pathways was noted in all patients on the MRI performed 3 months after surgery (Table 1).

#### Visual Acuity and Visual Fields

Visual field defect grade varied among patients, but more than half the patients (65.43%) showed a visual field defect of complete

<table>
<thead>
<tr>
<th>Table 1. Demographic Characteristics of Enrolled Patients</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Operation (number of patients)</td>
</tr>
<tr>
<td>Pathology (number of patients)</td>
</tr>
<tr>
<td>Sex ratio, M/F</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Preop tumor volume, cm³</td>
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<tr>
<td>Postop tumor volume, cm³</td>
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Table 2. Grading of Visual Field Defect

<table>
<thead>
<tr>
<th>Grade</th>
<th>Preop (n)</th>
<th>Postop 1 month (n)</th>
<th>Postop 3 months (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21.05% (4)</td>
<td>26.32% (5)</td>
<td>47.37% (9)</td>
</tr>
<tr>
<td>2</td>
<td>10.53% (2)</td>
<td>47.37% (9)</td>
<td>31.58% (6)</td>
</tr>
<tr>
<td>3</td>
<td>23.32% (5)</td>
<td>15.79% (3)</td>
<td>15.79% (3)</td>
</tr>
<tr>
<td>4</td>
<td>42.11% (8)</td>
<td>10.53% (2)</td>
<td>5.26% (1)</td>
</tr>
</tbody>
</table>

Grade 1 = quadrantanopsia, loss of vision in a quarter of the visual field; grade 2 = hemianopsia, partial loss of vision in half of the visual field; grade 3 = complete hemianopsia, complete loss of vision in half of the visual field; grade 4 = three quadrantanopsia or worse, loss of vision in three quarters of the visual field or worse, including blindness.

*Wilcoxon signed-ranks test between preoperative and postoperative 1-month measurements.
† Wilcoxon signed-ranks test between preoperative and postoperative 3-month measurements.

Photic Negative Response

RNFL thickness, GCC area, and PhNR/b-wave ratio were used to assess damage to retinal ganglion cells or retinal nerve fibers. All three parameters were reduced for 3 months and improved 6 months after surgery, and were significantly correlated with one another throughout the observation period (Fig. 5).

Correlation between OCT and PhNR

RNFL thickness, GCC area, and PhNR/b-wave ratio were used to assess damage to retinal ganglion cells or retinal nerve fibers. All three parameters were reduced for 3 months and improved 6 months after surgery, and were significantly correlated with one another throughout the observation period (Fig. 5).

Photopic Negative Response

PhNR/b-wave ratio in patients was significantly worse than that in normal controls (P = 0.011) before surgery and reduced continually at 1 and 3 months after surgery; however, these results did not reach the level of statistical significance (P = 0.212) (Table 3, Fig. 1). Like the OCT measurements, the PhNR/b-wave ratio also improved from 0.21 ± 0.11 at 3 months to 0.25 ± 0.11 at 6 months in 9 patients, although not significantly (P = 0.160) (Fig. 2).

Correlation between OCT and VF

MD was significantly correlated with the RNFL thickness of the temporal quadrant (linear; R² = 0.124, P = 0.010, logarithmic; R² = 0.103, P = 0.019) and inferior quadrant (linear; R² = 0.123, P = 0.005, logarithmic; R² = 0.137, P = 0.006). Temporal visual field sensitivity was also significantly correlated with temporal (R² = 0.350, P = 0.000) and inferior (R² = 0.218, P = 0.000) RNFL thickness (Table 4, Fig. 4).

The horizontal (linear; R² = 0.244, P = 0.000, logarithmic; R² = 0.218, P = 0.001), vertical (linear; R² = 0.257, P = 0.000, logarithmic; R² = 0.219, P = 0.001), and average (linear; R² = 0.219, P = 0.001), and average (linear; R² = 0.219, P = 0.001), and average (linear; R² = 0.219, P = 0.001).
0.245, \( P = 0.000 \), logarithmic; \( R^2 = 0.215, P = 0.001 \) values of the GCC area were significantly correlated with MD. Temporal visual field sensitivity was also significantly correlated with the horizontal (\( R^2 = 0.318, P = 0.000 \)), vertical (\( R^2 = 0.224, P = 0.001 \)), and average (\( R^2 = 0.198, P = 0.002 \)) values of the GCC area (Table 4, Fig. 4).

The PhNR/b-wave ratio was correlated with MD (logarithmic; \( R^2 = 0.110, P = 0.026 \)) and temporal visual field sensitivity (\( R^2 = 0.286, P = 0.000 \)) (Table 4, Fig. 4).

**DISCUSSION**

**Correlation between VF and OCT**

The RNFL thickness of temporal and inferior quadrant correlated significantly with VF. The horizontal and average values of the GCC area were also significantly correlated with VF. Chiasm compression produces visual field defects principally in the temporal hemifield. The temporal visual field defect is a

**FIGURE 1.** Changes in RNFL thickness (A), GCC area (B), and PhNR/b-wave ratio (C) after surgical decompression. Data points indicate mean ± SD. *\( P < 0.05 \), **\( P < 0.01 \), ***\( P < 0.001 \); tested by Wilcoxon signed-ranks test. †\( P < 0.05 \), ††\( P < 0.01 \), †††\( P < 0.001 \); tested by Mann–Whitney test.

**FIGURE 2.** Changes in average RNFL thickness (A), average GCC area (B), and PhNR/b-wave ratio (C) after surgical decompression in nine patients who underwent a 6-month follow-up. Average data points indicate mean ± SD.
Table 4. Coefficient of Determination ($R^2$) of Regression between Visual Fields and OCT Measurements and PhNR/b-wave Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Deviation (dB)</th>
<th>Temporal Hemifield (1/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear R²  P</td>
<td>Logarithmic R²  P</td>
</tr>
<tr>
<td>RNFL thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior</td>
<td>0.013  0.424</td>
<td>0.016  0.364</td>
</tr>
<tr>
<td>Inferior</td>
<td>0.123  0.005***</td>
<td>0.137  0.006††</td>
</tr>
<tr>
<td>Nasal</td>
<td>0.015  0.385</td>
<td>0.007  0.553</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.124  0.010*</td>
<td>0.103  0.019†</td>
</tr>
<tr>
<td>Average</td>
<td>0.074  0.049*</td>
<td>0.069  0.058</td>
</tr>
<tr>
<td>GCC area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>0.244  0.000***</td>
<td>0.218  0.001††</td>
</tr>
<tr>
<td>Vertical</td>
<td>0.237  0.000***</td>
<td>0.219  0.001††</td>
</tr>
<tr>
<td>Average</td>
<td>0.245  0.000***</td>
<td>0.215  0.001††</td>
</tr>
<tr>
<td>PhNR/b-wave ratio</td>
<td>0.066  0.087</td>
<td>0.110  0.026</td>
</tr>
</tbody>
</table>

$^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$: linear regression value.
$^†P < 0.05$, $^{††}P < 0.01$, $^{†††}P < 0.001$: logarithmic regression value.

Correlation between VF and PhNR

The PhNR/b-wave ratio was significantly correlated with VF. PhNR is a negative wave that follows the photopic b-wave. PhNR originates from the activity of RGCs, which receive signals from cones.11 The PhNR is strongly attenuated in primary eyes with experimentally induced glaucoma and in eyes intravitreally injected with tetrodotoxin, which blocks the neural activity of retinal ganglion cells and their axons.25–27 Investigators have been reporting that the PhNR can be used to evaluate the inner retina in patients with optic nerve disease.27–30 It was reported that PhNR was reduced and correlated significantly with RNFL thickness in 10 patients with optic nerve atrophy.30 In this study, the PhNR/b-wave ratio was significantly correlated with VF as well as RNFL thickness and the GCC area, which suggests that in chiasmal compression, the PhNR can serve as an indicator for evaluating the degree of damages in RGCs. Moreover, PhNR is relevant as a functional indicator compared with the OCT, which reflects structural changes.

The pattern electroretinogram (PERG) is another electrophysiological examination that reflects inner retinal function and also originates from the activity of retinal ganglion cells. Several studies of PERG have been performed in patients with chiasmal compression.9,10 It was reported that the PERG is a useful visual prognostic indicator in one study. However, in that study, visual fields were assessed (with Goldmann perimetry) and estimated only in 5°, and the prognostic value of PERG was not high either.9 One study using SAP, OCT, and PERG showed that PERG amplitude, time domain OCT macular thickness, and RNFL thickness were all significantly related to visual field loss. The relationship between PERG amplitude and OCT thickness measurements was not significant.10 In the present study, visual field was assessed quantitatively using SAP and PhNR evidenced a significant correlation throughout the observation periods. Besides, the PhNR/b-wave ratio was significantly correlated with RNFL thickness and GCC area measurements using SD-OCT. This suggests that the PhNR can be used as an indicator for evaluating the degree of damages in RGCs and is somewhat more reliable than PERG in chiasmal compression.

Additionally, PhNR has advantages relative to PERG from several practical perspectives. PhNR is not necessary to correct the refractive errors, does not require fixation or exact foveal placement, and is relatively unaffected by the opacity of the ocular media because PhNR is elicited by a strong flash.11,30

Time Difference between Changes of VF and RGCs

In the present study, RNFL thickness, GCC area, and PhNR/b-wave ratio showed a significant positive correlation with VF. However, VF significantly improved for 3 months after surgery, whereas RNFL thickness, GCC area, and PhNR/b-wave ratio
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were reduced. The two results mentioned earlier can be misunderstood as incompatible, but are actually attributable to the time difference between changes in the VF and RGCs. The aspect of changes in VF and RGCs along the course of time and their differences are described in a diagram involving the mechanisms responsible for it (Fig. 5).

Visual field changes may precede ganglion cell loss in compression syndrome. When a chiasmal tumor has grown large enough and compresses the anterior visual pathway, an immediate physiologic conduction block may occur, thus resulting in visual dysfunction. If decompression is not achieved, reversible or irreversible axonal injuries to the optic nerve and resultant visual dysfunction will progress, and retinal nerve fibers and RGCs could also be damaged by axonal injury. However, there is a time difference between changes in the visual field and RGCs, since damage to RGCs does not occur via a direct process, but rather is the consequence of retrograde degeneration and thus takes some time to occur.

The time difference between axonal injury and after loss of RGCs has been proven with animal experiments. In one study, when the site of axonal injury was further from the globe and the injury was relatively less profound, the latency to the onset of ganglion cell loss was longer and fewer ganglion cells were lost. Additionally, ganglion cell atrophy was prolonged for various times from 3 to 6 months. After decompression surgery, improvements in the visual field may also precede the restoration of RGCs. Immediate recovery of visual function results from the removal of the physiologic conduction block and the restoration of signal conduction. However, the significant reductions in RNFL thickness, GCC area, and PhNR/b-wave ratio observed for 3 months after surgery in the present study indicate that prolonged retrograde degeneration progressed for some period, even after decompression surgery. Delayed restoration of RGCs may take place when active remyelination has occurred. During that period, axoplasmic flow restoration also occurs, resulting in additional improvements of visual function. Recently, it was reported that a thickening of RNFL occurred after surgery in patients with parachiasmal tumors. Patients undergoing surgical resections of parachiasmal lesions were evaluated before surgery with SAP and RNFL thickness, using OCT. Tests were repeated within 6 weeks after surgery. RNFL thickness significantly increased, by 1%, after surgery among all eyes. This result corresponded to the findings of the present study. More delayed restoration of retinal structure in our study may be associated with the difference of severity in visual field defects, preoperatively. In the previous study, the average MD of enrolled patients was $-9.6 \pm 9.8$ dB, but was $-16.75 \pm 9.04$ dB in ours. A more severely affected optic nerve and visual function may result in more prolonged degeneration and delayed restoration of retinal structure.

The findings of this study suggest that changes in the VF and RGCs show a similar time course aspect, but occur at different time points.

**FIGURE 4.** Scatterplot of MD and temporal RNFL thickness (A), horizontal GCC area (B), and PhNR/b-wave ratio (C). Scatterplot of temporal visual sensitivity (1/L) and temporal RNFL thickness (D), horizontal GCC area (E), and PhNR/b-wave ratio (F).
Limitation of the Present Study

The principal limitation of this study was its small number of participants. However, the patients who met the inclusion criteria were strictly followed-up prospectively. Further investigations with extended individuals and prolonged periods will be required.

CONCLUSIONS

Visual field recovery and changes in RGCs after chiasmal decompression evidence a similar aspect and are significantly correlated. However, prolonged retrograde degeneration progressed for some period, even after surgical decompression and visual field recovery precedes the demonstrable retinal regeneration.

References

18. Danesh-Meyer HV, Carroll SC, Foroozan R, et al. Relationship between retinal nerve fiber layer and visual field sensitivity as...


