Quantitative Evaluation of Papilledema in Pseudotumor Cerebri

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**PURPOSE.** To determine the feasibility of adapting confocal scanning laser (CSL) tomography of the optic disc for quantitative evaluation of papilledema in pseudotumor cerebri (PTC).

**METHODS.** Confocal scanning laser tomography of the optic disc was performed in 11 patients with diagnosed PTC and 12 visually normal control subjects of similar age. In five patients with active papilledema, CSL tomography was performed serially over several months. To quantify optic disc characteristics, surface topography was measured in 0.1-mm steps along the horizontal and vertical meridians and four oblique meridians. Best fit polynomial functions, describing surface topography along each meridian, were derived using linear regression analysis.

**RESULTS.** Third-order polynomials provided excellent fits (significantly better than the second-order functions) to the surface topography for all meridians in the control subjects and patients with PTC. In control subjects and PTC patients an asymmetry in the slope of the optic disc contours was evident along the horizontal but not the vertical meridian. In patients with active papilledema a significant elevation of the center of the disc was accompanied by a change in overall surface topography. Each of the PTC patients followed up serially had a pronounced posterior deformation of the disc (i.e., a reduction in papilledema) that was initially apparent in the temporal meridian and did not proceed uniformly across all meridians.

**CONCLUSIONS.** Confocal scanning laser tomography can quantify the magnitude and monitor the resolution of papilledema in PTC. Studies of optic nerve head topography may provide further insight into optic nerve compliance with elevated intracranial pressure. (Invest Ophthal Mol Vis Sci. 1998;39:1964–1971)

Papilledema refers to swelling of the optic disc produced by elevated intracranial pressure. Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension, is a central nervous system disorder that can produce papilledema. Clinical detection of papilledema in PTC requires skilled ophthalmoscopic evaluation of the optic disc and peripapillary nerve fiber layer. Obscuration of the peripapillary nerve fiber layer as it crosses the disc margins is considered evidence of early swelling. Unfortunately, ophthalmoscopic evaluation is subjective and inexact, and early or subtle changes in optic disc and nerve fiber layer morphology may be missed. Stereo disc photography and fluorescein angiography increase the precision of disc and nerve fiber layer evaluation, but their interpretation remains primarily subjective, qualitative, and imprecise.

In recent years, considerable progress has been made in developing noninvasive techniques for imaging retinal structures. In particular, confocal scanning laser (CSL) tomography holds great promise as a reliable, reproducible method to quantify the three-dimensional topography of the optic nerve head. In several studies, the sensitivity and reliability of this method have been examined for the early detection of changes in optic nerve head morphology in patients with suspected glaucoma. Other investigators have evaluated the utility of the CSL technique for monitoring the progression of optic disc changes in patients with established glaucoma. Consequently, many technical issues regarding the use of CSL tomography for quantitative study of the optic nerve head and the peripapillary nerve fiber layer have been investigated previously. As an initial step in examining the feasibility of adapting CSL tomography for the assessment of papilledema in PTC, we intended to determine whether the technique could be used to quantify differences in optic nerve topography between patients with papilledema and control subjects.

**MATERIALS AND METHODS**

**Imaging**

A confocal microscope with attached scanning laser (The Heidelberg Retina Tomograph [HRT]; Heidelberg Engineering, Heidelberg, Germany) was used to image the optic disc. The HRT uses a 650-nm diode laser to scan the retinal surface in three dimensions. To generate three-dimensional tomography images, the HRT acquires a series of transverse optic sections taken at 32 consecutive equally spaced focal planes over a scan depth that can be adjusted from 0.5 mm to 4.0 mm. These images are obtained very rapidly (total acquisition time, approximately 1.6 seconds for the 32 images). Each optic section image is generated from a 256 × 256 pixel matrix (65,536 pixels) in which each pixel represents the elevation (or height of the retinal surface) at a specific location. The section images are automatically aligned for horizontal and vertical shifts caused by any fixation instability during image acquisition. By combining the images in each series, the software generates a topographic map (also containing 256 × 256 pixels), in which
FIGURE 1. An illustration of the specific locations used in the topographic analysis. Mean retinal elevation was calculated for each of 16 positions (determined in 0.1-mm steps from 0.2 mm to 1.7 mm) along each of 12 meridians, ranging from 0° (temporal) to 330° in 30° steps. At each of these positions the retinal elevation was calculated as the mean surface elevation along the circumference of a concentric ring having the same radius as the location and extending ±15° from each meridian.

Each pixel has a value describing surface elevation at that particular point. The elevation values are expressed relative to a reference plane, which in this study was chosen to be the focal plane of the eye (see description later).

A 15° X 15° image, centered relative to the optic disc, was chosen for all images obtained in the study. Images were acquired using the standard HRT protocol (version 1.11; Heidelberg Engineering) in which the elevation of the retinal surface is calculated relative to a reference plane placed 50 μm posterior to the mean retinal elevation along a circle concentric with the optic disc margin in the temporal segment between 350° and 356°. Three topographic images were obtained through the undilated pupil of each eye, and every image was corrected for tilt using a reference ring placed along the margin on the topographic image with an outer diameter of 94% of image size. A mean image created by averaging three images from each eye was used for analysis. Images were taken from both eyes, but only data from the right eyes are included in this report.

To further refine the analysis, the HFT data were transformed as follows. With 0° defined as temporal, 12 meridians were selected for analysis. (Fig. 1). The twelve meridians ranged from 0° to 330° in 30° steps. Mean retinal elevation was then calculated for each of 16 positions along each meridian, determined in 0.1-mm steps from 0.2 mm to 1.7 mm. At each of these positions the retinal evaluation was calculated as the mean surface elevation along the circumference of a concentric ring having the same radius as the location and extending ±15° from each meridian, as indicated in Table 1. The mean retinal elevation at each position was then expressed relative to the mean elevation determined for a ±5° arc centered at a radius of 1.7 mm along the 0° meridian (i.e., each mean elevation was normalized relative to this reference value).

Subjects

Optic nerve head images were collected from 12 visually normal, healthy subjects (control subjects) ranging in age from 23 to 47 years (mean age, 33.0 ± 7.2 years) and from 11 patients with PTC (idiopathic intracranial hypertension) ranging in age from 21 to 55 years (mean age, 34.5 ± 10.2 years). Individuals with more than 5 diopters (D) of myopia, more than 2.0 D of hyperopia or more than 1.0 D of astigmatic error were excluded. Individuals with a history of ophthalmic disease or systemic disease with ocular manifestations were also excluded. The patient group included seven patients in the active stage of the disease (mean age, 36.4 ± 12.1 years) and four with clinically resolved disease (mean age, 31.0 ± 5.5 years). A patient was considered to have clinically resolved papilledema if on clinical evaluation the optic nerve head and visual fields had a stable, unchanging appearance over a 6 month period and if the patient was asymptomatic while not receiving treatment (with the exception of known visual loss that had occurred during the active phase of the disease). All the patients with PTC had had normal findings in computed tomographic scans and had undergone lumbar puncture, which showed cerebrospinal fluid pressure of more than 200 mm Hg, fewer
TABLE 1. Best Fit Third-Order Polynomial Functions

<table>
<thead>
<tr>
<th>Meridian</th>
<th>Mean Retinal Elevation Used in Computation</th>
<th>Control Subjects</th>
<th>Active Papilledema</th>
<th>Clinically Resolved Papilledema</th>
</tr>
</thead>
<tbody>
<tr>
<td>0° Temporal</td>
<td>345-359° and 0-15°</td>
<td>-0.937 ± 1.589x - 0.856x² + 0.145x³</td>
<td>-0.216 ± 1.253x - 0.900x² + 0.136x³</td>
<td>-0.256 ± 1.009x - 0.965x² + 0.272x³</td>
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<tr>
<td>30°</td>
<td>15-45°</td>
<td>-0.897 ± 1.834x - 1.011x² + 0.170x³</td>
<td>-0.291 ± 1.628x - 1.075x² - 0.151x³</td>
<td>-0.260 ± 1.008x - 0.792x² + 0.184x³</td>
</tr>
<tr>
<td>60°</td>
<td>45-75°</td>
<td>-1.090 ± 2.430x - 1.552x² + 0.318x³</td>
<td>-0.332 ± 2.101x - 1.403x² + 0.228x³</td>
<td>-0.315 ± 1.345x - 0.960x² + 0.199x³</td>
</tr>
<tr>
<td>90° Superior</td>
<td>90-105°</td>
<td>-1.161 ± 3.011x - 2.215x² + 0.521x³</td>
<td>-0.374 ± 2.689x - 2.095x² + 0.438x³</td>
<td>-0.349 ± 1.742x - 1.316x² + 0.281x³</td>
</tr>
<tr>
<td>120°</td>
<td>105-135°</td>
<td>-1.118 ± 3.158x - 2.529x² + 0.646x³</td>
<td>-0.298 ± 3.084x - 2.736x² + 0.672x³</td>
<td>-0.381 ± 2.304x - 2.117x² + 0.574x³</td>
</tr>
<tr>
<td>150°</td>
<td>135-165°</td>
<td>-1.046 ± 3.068x - 2.591x² + 0.693x³</td>
<td>-0.202 ± 3.061x - 2.971x² + 0.792x³</td>
<td>-0.386 ± 2.640x - 2.706x² + 0.774x³</td>
</tr>
<tr>
<td>180° Nasal</td>
<td>165-195°</td>
<td>-1.013 ± 3.077x - 2.722x² + 0.757x³</td>
<td>-0.126 ± 3.006x - 3.146x² + 0.085x³</td>
<td>-0.385 ± 2.881x - 3.197x² + 0.970x³</td>
</tr>
<tr>
<td>210°</td>
<td>195-225°</td>
<td>-1.034 ± 3.136x - 2.717x² + 0.744x³</td>
<td>-0.089 ± 2.813x - 2.906x² + 0.807x³</td>
<td>-0.367 ± 2.755x - 2.959x² + 0.877x³</td>
</tr>
<tr>
<td>240°</td>
<td>225-255°</td>
<td>-1.099 ± 3.263x - 2.651x² + 0.687x³</td>
<td>-0.125 ± 2.725x - 2.643x² + 0.697x³</td>
<td>-0.351 ± 2.444x - 2.321x² + 0.626x³</td>
</tr>
<tr>
<td>270° Inferior</td>
<td>255-285°</td>
<td>-1.125 ± 2.986x - 2.226x² + 0.527x³</td>
<td>-0.170 ± 2.386x - 2.003x² + 0.450x³</td>
<td>-0.326 ± 2.001x - 1.690x² + 0.408x³</td>
</tr>
<tr>
<td>300°</td>
<td>285-315°</td>
<td>-1.012 ± 2.133x - 1.335x² + 0.277x³</td>
<td>-0.196 ± 1.886x - 1.446x² + 0.292x³</td>
<td>-0.292 ± 1.540x - 1.313x² + 0.325x³</td>
</tr>
<tr>
<td>330°</td>
<td>315-345°</td>
<td>-0.944 ± 1.677x - 0.952x² + 0.180x³</td>
<td>-0.202 ± 1.477x - 1.147x² + 0.219x³</td>
<td>-0.267 ± 1.215x - 1.112x² + 0.296x³</td>
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</table>

PTC, pseudotumor cerebri.

The specific locations at which retinal surface elevation was determined are shown along with the equations for the best fit third-order polynomial functions relating retinal surface elevation to distance from the center of the optic disc (x) in the control subjects (n = 12), patients with PTC with active papilledema (n = 7), and patients with PTC with resolved papilledema (n = 4).
Patients with PTC with Active Papilledema

In the patients with PTC with active papilledema the elevation of the retinal surface was at its maximum between 0.7 mm and 1.0 mm (i.e., near the location of the disc margin in the control group) and decreased inside and beyond this region (Fig. 2). This pattern was evident in all the patients with active papilledema, although it was more obvious along some meridians (e.g., 90°) than along others (e.g., 0°). This finding suggests differential swelling along the various meridians. The patients with PTC with active papilledema also had a pronounced asymmetry in the topography of the optic disc in different meridians that was most apparent along the horizontal meridian (Fig. 2, left) and that exceeded the asymmetry noted for this meridian in the control group. In contrast, along the vertical meridian, the contour of the disc was very similar for superior and inferior meridians (Fig. 2, right).

The mean surface elevation as a function of distance from the center of the optic disc was calculated in the patients with active papilledema, and polynomial regressions were used to describe surface elevation along each meridian as a function of distance from the center of the optic disc. Polynomial regressions were used to relate surface elevation to distance from the center of the optic disc (Figs. 3, 3B, 3C). Second-order polynomial functions produced good fits for most meridians, ranging from a minimum of $R^2 = 0.864$ (at 180°) to a maximum of $R^2 = 0.993$ (at 0° and 330°). The fits were least satisfactory for the nasal meridians (150° to 210°). Third-order polynomials provided excellent fits for all meridians ($R^2 > 0.98$, in every case); the third-order polynomial functions fit the data significantly better than the second-order functions ($t$-test; $P = 0.005$).
FIGURE 3. Mean relative surface elevation was plotted as a function of distance from the center of the optic disc in the three patient groups. (A) Relative surface elevation along the horizontal meridian, (B) relative surface elevation along the vertical meridian, and (C) relative surface elevation along each of the other meridians.
distance from the center of the optic disc (Figs. 3A, 3B, 3C). Second-order polynomial functions provided good fits for most meridians, ranging from a minimum $R^2 = 0.848$ (at 180°) to a maximum $R^2 = 0.970$ (at 60°). The fits were least satisfactory ($R^2 < 0.90$) for the nasal and inferior nasal meridians (150-240°). Third-order polynomial functions fit the data for all meridians extremely well ($R^2 > 0.98$ in all meridians except 0° and 330°, where $R^2 = 0.935$ and $R^2 = 0.951$, respectively). The third-order functions fit the data significantly better than the second-order function ($t$-test; $P = 0.005$).

**Patients with PTC with Clinically Resolved Papilledema**

In the patients with PTC with clinically resolved papilledema, retinal surface elevation was also at its maximum between 0.7 mm and 1.0 mm (in the region of the normal disc margin) and decreased within and beyond this region (Fig. 2). However, in two patients this trend was not evident temporally (i.e., along the 0°, 30°, and 330° meridians). Instead, in these patients the retinal surface appeared to be essentially flat along these meridians. As was the case in the other two groups, an asymmetry in the slope of the optic disc contours along the horizontal meridian was evident in the patients with PTC with clinically resolved papilledema (Fig. 2, left). No asymmetry was noted in the vertical meridian (Fig. 2, right).

The mean surface elevation as a function of the distance from the center of the optic disc was calculated in the patients with PTC with resolved papilledema, and polynomial regressions were fit to the results (Figs. 3A, 3B, 3C). Second-order polynomial functions fit the data well ($R^2 > 0.90$) along several of the meridians (0°-90° and 270°), but the second-order functions were less satisfactory for the superior and inferior nasal meridians ranging from a minimum of $R^2 = 0.722$ at 180° to 0.852 at 120°. Third-order polynomial functions provided very good fits for all meridians ($R^2 > 0.95$, in every case) and the third-order functions fit the data significantly better than the second-order functions ($t$-test; $P = 0.005$).

**Comparison of Optic Disc Topography between Different Groups**

In the patients with active papilledema, the intercept of the best fit third-order polynomial functions varied systematically as a function of the meridian measured. The intercept was lowest in the inferior nasal quadrant (180-270°) and greatest at the superior region (60-120°; Table 1). This is distinct from the findings in the control group where the intercepts were lowest in the temporal quadrant and greatest along the vertical meridian (Table 1). Statistical analysis confirms that in the patients with active papilledema the intercepts were significantly less negative (more anterior) than in the control group ($t$-test; $P \leq 0.005$). This was true in each of the 12 meridians. This result suggests an increased elevation (i.e., an anterior displacement) at the center of the optic disc in patients with active papilledema. This elevation ranged from 0.696 mm (at 30°) to 0.974 mm (at 240°).

In the patients with clinically resolved papilledema, the intercept of the best fit third-order polynomial functions also varied systematically as a function of the meridian examined: The intercept was lowest in the inferior region (150-210°) and greatest in the temporal region (0°, 30°, and 330°; Table 1). However, the magnitude of this displacement, ranging from 0.628 mm (180°) to 0.799 mm (270°), was consistently less than in the patients with active papilledema. Statistical analysis confirmed that in the patients with clinically resolved papilledema the intercepts were significantly ($P \leq 0.005$) less negative (more anterior) than in the control group for all meridians except nasally (150-210°) where $P \geq 0.01$.

To determine whether the elevation of the center of the optic disc was accompanied by a change in overall shape of the disc, an analysis of variance was used, and the coefficients of the first-, second- and third-order terms of the best fit cubic regressions were assessed. Statistically significant differences were detected in the control subjects when compared with the patients with active papilledema and the patients with clini-
The initial objective of this study was to determine whether partial in other meridians in three patients, and was partial Remission of Papilledema glion cell degeneration that occurs in glaucoma. As a result, all meridians except 90°, 240°, and 300°. This was done by measuring retinal surface elevation at specific distances from the center of the optic disc along selected meridians and averaging values for a series of points adjacent to either side of these meridians. Consequently, the magnitude of the data set and the measurement variability were reduced.

Using this technique, we have shown that it is not only possible to image optics discs with papilledema but that it is possible to use these images to quantify the changes in topography associated with disc swelling and its resolution. We found that compared with the topography of the optic disc in control subjects, patients with PTC with active papilledema had a significant elevation of the center of the disc and a change in its overall topography (Fig. 4). Along most meridians the retinal topography was adequately described by a second-order polynomial function. However, in all patient groups the contours were represented better by a third-order polynomial function. This observation suggests that at least in some meridians (e.g., nasal and inferior), an additional factor is required to describe adequately the change in curvature of the topographic surface. One possible interpretation of this result is that either the underlying anatomic structure of the optic nerve head or the structural constraints on the nerve itself are not uniformly distributed along all meridians. Furthermore, the anatomic structure and the structural constraints on the optic nerve head may be differentially affected by the forces that produce papilledema. This possibility requires further evaluation.

Reliable quantitative analysis of papilledema facilitates comparisons between groups. In this case a quantitative comparison showed that optic nerve head topography was not normal in patients with clinically resolved papilledema and that it also differed from the topographic pattern characteristic of patients with active papilledema. The abnormal disc topography in patients with resolved papilledema could have reflected residual optic disc swelling or the long-term development of structural changes such as scarring, stretching, and gliosis. Reliable quantitative analysis also facilitated monitoring the progression–remission of papilledema. In each of the five patients who were followed up serially we were able to show some resolution of disc swelling, although it was incomplete in most cases. We also noted asymmetries in swelling and its resolution that may reflect constraints on optic nerve head displacement in response to elevated intracranial pressure or altered transmammary tissue pressure gradients. Hayreh and Hayreh observed an asymmetric evolution and resolution of papilledema in a primate model of optic disc edema in which intracranial pressure was elevated by inflating a balloon placed in the subarachnoid space. In our observations and in the results of Hayreh and Hayreh, the least optic disc edema developed in the temporal meridian (Figs. 2, 3), and optic disc edema resolved first in that same area. In the primate model, however, edema was greater superiorly and inferiorly than nasally, whereas we found little if any difference in the degree of edema between the superior, inferior, or nasal meridians.

Our findings show the feasibility of using CSL tomography to measure and quantify papilledema and also suggest the need for additional studies. A masked comparison between CSL tomography and stereophotography of the optic disc should be conducted to determine the clinical utility of this technique. In addition, a long-term longitudinal study is required to relate changes in optic disc topography to the eventual development and progression of functional deficits in patients with PTC. Finally, our results suggest that it may be possible to evaluate the relationships between papilledema and intracranial pressure by quantitatively assessing changes in optic disc topography in patients with abnormal intracranial pressure.

References
Ultrastructural Changes in Rabbit Ciliary Body after Extraocular Mitomycin C

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PURPOSE. To study the ultrastructural changes in ciliary body epithelium of the rabbit eye after subconjunctival injections of mitomycin C.

METHODS. One eye of six New Zealand white rabbits was given a subconjunctival injection at the 12-o’clock position with 0.005, 0.02, 0.08, 0.1, 0.12, or 0.16 mg mitomycin C. The fellow eye was given a subconjunctival injection of balanced salt solution. Two weeks after treatment, the eyes were enucleated, and the ciliary body was exposed and submerged in fresh 4% paraformaldehyde/2% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4, at 4°C. Electron microscopy of the ciliary body was performed at two sites: the injection site (12-o’clock position) and 180° away (6-o’clock position).

RESULTS. At dosages of 0.1 mg and higher, ciliary body epithelial cells beneath the injection site were thinned. There were vacuoles and expansion of intracellular and intercellular spaces. Plasma membrane infoldings were disrupted, and the apical membrane was thinned. Mitochondria and nuclei were normal. Ciliary body epithelium at 6-o’clock position were normal. Ciliary body epithelium at 6-o’clock position were thinned. Mitochondria and nuclei were normal. Ciliary body epithelium at 6-o’clock position were thinned. Mitochondria and nuclei were normal. There were vacuoles and expansion of intracellular and intercellular spaces. Plasma membrane infoldings were disrupted, and the apical membrane was thinned. Mitochondria and nuclei were normal.


Mitomycin C (MMC), an antibiotic isolated from Streptomyces caesuis with antiproliferative activity against fibroblasts,1 has gained popularity as adjunctive therapy during glaucoma filtration surgery. Proposed mechanisms of improved success with MMC filtration surgery include decreased resistance to outflow with thinner blebs2 and cytotoxic ciliary body effects leading to decreased aqueous humor production.3 Extraocular application of MMC in the rabbit model has produced contradictory results. Some investigators have demonstrated direct cytotoxic effects of MMC on the ciliary body epithelium,4 whereas others have not.5 Given the frequency of MMC use during trabeculectomy and the higher incidence of hypotony after filtration surgery with this agent,6 we sought to delineate more clearly the possible role of MMC in ciliary body damage.

METHODS

Mitomycin C (Bristol Myers Squibb Oncology, Princeton, New Jersey) was reconstituted in sterile balanced salt solution. One eye from each of six New Zealand White rabbits was given a 0.1-ml subconjunctival injection at the 12-o’clock position on the eye of either 0.05, 0.20, 0.80, 1.0, 1.2, or 1.6 mg/ml MMC. The fellow eye was given a 0.1-ml injection of balanced salt solution. The rabbits were anesthetized with ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (5 mg/kg) before subconjunctival injections. All handling of the rabbits was in compliance with the University of Virginia Animal Research Committee Protocol and the ARVO Guidelines on Use of Animals in Ophthalmic and Vision Research. Tobramycin and dexamethasone sterile ophthalmic solutions were instilled in each eye 4 times a day for 1 week. At the end of 2 weeks, the rabbits were euthanized. All treated and control eyes were enucleated. Immediately after enucleation, the eyes were biected to maximally expose the ciliary bodies and submerged in fresh 4% paraformaldehyde/2% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4, at 4°C. After fixation, segments of the ciliary body at the injection site superiorly and 180° away (6-o’clock position) were dissected and routinely processed for electron microscopy through 2% osmium tetroxide, ethanol dehydration, and infiltration and embedding in epoxy resin. Ultrathin sections (70-80 nm in thickness) were counterstained with lead citrate and uranyl acetate and examined in an electron microscope (model JEOL 100-CX; Japan Electron Optics Limited, Tokyo, Japan).