Correlation of Optic Nerve Head Tomography with Visual Field Sensitivity in Papilledema

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Purpose. To quantify the relationship between optic nerve head tomography and perimetric sensitivity in patients with papilledema.

Methods. Eight patients with variable degrees of recently diagnosed papilledema associated with idiopathic intracranial hypertension (IIH) were evaluated with confocal scanning laser ophthalmoscopy (CSLO) and automated perimetry. Patients were followed up with serial measurements over a period of 5 to 30 months (mean ± SD, 17.1 ± 9), while under medical treatment (acetazolamide). The tomographic parameters, volume above reference (VAR), volume above surface (VAS), effective mean height (EMH), and maximum height in contour (MxHC), were obtained by tomography, either globally or from predefined disc sectors. The perimetric indices, mean deviation (MD) and pattern standard deviation (PSD), were evaluated. The results from patients’ right eyes and the individual intereye differences in both tomographic and perimetric parameters, were statistically evaluated by nonparametric correlational (Spearman) and repeated measures (Wilcoxon) analyses.

Results. At baseline, all tomographic parameters were negatively correlated with MD in global (r = −0.8) and sectorial (r = −0.6) evaluations. The interocular differences in overall tomographic parameters were correlated with corresponding differences in perimetric MD (r = −0.8) and PSD (r = 0.6). During the follow-up period, volumetric disc parameters decreased (P < 0.02), whereas perimetric MD increased (P = 0.02) at comparable times.

Conclusions. In patients with recently diagnosed papilledema, optic nerve head tomographic abnormalities are quantitatively correlated with visual field sensitivity losses. Therapeutic improvement of volumetric parameters may be paralleled by recovery in perimetric sensitivity. The data support the possible use of both techniques in combination to monitor the amount of papilledema and the effectiveness of treatments designed to reduce intracranial hypertension. (Invest Ophthalmol Vis Sci. 2001;42:1487–1494)

During the past few decades several approaches have been used to analyze the papilledema from intracranial hypertension either functionally1−5 or morphologically.6–20 Among the functional techniques, electrophysiology of the optic nerve (pattern evoked potentials and pattern electroretinogram),2,5,7 pupil response testing,6 contrast sensitivity testing,1−5,8,9 automated threshold perimetry,3,4,8,9 motion perimetry,9 and high-pass resolution perimetry4,9 have been used. The prominent role of automated perimetry in detecting the earliest functional losses and following up the progression of dysfunction has been stressed by different studies.3,5,6,21 Morphologic techniques include ophthalmoscopic examination,11 fluorescein angiography,10 optic disc and retinal nerve fiber layer photography,9,15 stereoscopic color photography,10 echographic transverse optic nerve diameter measurements,12,13 computed tomography (CT),14 magnetic resonance imaging (MRI),20 and, recently, confocal scanning laser ophthalmoscopy (CSLO).16−19 In papilledema due to idiopathic intracranial hypertension (IIH), reliability of CSLO as a quantitative method of evaluating disc swelling has been demonstrated.17−19

The correlation between optic disc morphology and visual field sensitivity in papilledema has not been quantitatively determined, although qualitative associations have been reported.3,5,7,17,22–25 Establishing such a correlation could strengthen the diagnostic utility of both methods in diagnosis and follow-up of papilledema. The purpose of the present study was to evaluate whether, and to what extent, the degree of disc swelling, as measured by CSLO tomographic parameters, correlates quantitatively with the severity of visual dysfunction, determined by automated perimetry. To this end, correlations were evaluated in the same patients either cross-sectionally or longitudinally. The results show a close association between optic nerve tomography and visual field sensitivity in recently diagnosed papilledema.

Methods

Subjects

The patients enrolled in the study were recruited from larger cohorts of patients evaluated at the Neuro-Ophthalmology Service of our institution. Both eyes of eight patients (four men, four women; mean age ± SD: 41.1 ± 12.3 years), with ophthalmoscopic evidence of a variable degree of disc swelling and a clinical diagnosis of IIH, were examined with both CSLO tomography and automated perimetry. Testing was performed at the time of diagnosis and at various times during a clinical follow-up of variable length (described later). The test schedule and demographic and clinical data are summarized in Table 1. The diagnosis was based on the modified Dandy criteria, reported by Smith26: signs and symptoms of increased intracranial pressure in an alert and awake patient, normal neurologic examination findings except for papilledema and its associated visual loss and sixth nerve palsies, normal findings in neurodiagnostic studies except for increased cerebrospinal fluid (CSF) pressure (>250 mm H2O), and no secondary cause of intracranial hypertension. All patients had normal neurodiagnostic evaluation by CT brain scanning and MRI. CSF pressure measured in patients by lumbar puncture ranged from 260 to 320 mm H2O. Direct ophthalmoscopic and 90-diopter (D) lens biomicroscopic assessment of the degree of papilledema was based on the staging scheme proposed by Frisen11: the whole range of disc swelling from stage 0 (normal optic disc) to stage 5 (marked disc swelling) was represented in the patient group. None of them showed signs of atrophic papilledema, such as marked pallor, gliosis, and vessel attenuation. Additional inclusion criteria were good compliance, clear CSLO

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images of the optic nerve head (average variability <30 μm), reliable visual fields,37 (at least two Humphrey 30-2 threshold tests [Allergan-Humphrey, San Leandro, CA] within 5 days), refractive errors comprised between −5.50 and +2.00 D spherical equivalent, astigmatism less than ±1.00 D, and absence of other disorders affecting the optic disc or visual field. Best corrected visual acuity was 20/20 in all but one eye in one patient (20/30 in the left eye of patient 7, Table 1).

Patients were studied serially during the course of a follow-up period ranging from 5 to 30 months (mean = 17.1 ± 9). All patients were under medical treatment (oral acetazolamide, 500-1000 mg twice daily) during the follow-up, with temporary (suspension periods. At each follow-up session, tomographic analysis was performed on the same day of the first perimetric examination by a different operator, masked as to the patient’s characteristics and clinical information. Sometimes, measurement sessions had to be limited to only one eye of a patient because of fatigue. Both the tomographic (Heidelberg Retinal Tomograph [HRT]; Heidelberg Engineering, Heidelberg, Germany) and field measurements were unavailable for the left eye of patient 4 at visit 3, whereas visual field data were unavailable for both eyes of patients 3 and 8 at visits 3 and 6, respectively; and for the left eye of patient 2 at visit 2. Informed consent was obtained from every patient, after the procedures to be performed by the manufacturer (STATPAC; Allergan-Humphrey). All patients were experienced in automated threshold perimetry, and results were analyzed beginning with the second visual field examination.

Test-retest variability of the three measurements of each point, expressed by the average of the SDs of the topographic values of each pixel in the three images, was 17.84 ± 6.93 μm (range: 7.73–29.91) for right eyes and 19.59 ± 6.44 μm (range: 8.85–27.27) for left eyes.

Automated Static Perimetry. Visual field analysis was performed on the Humphrey field analyzer model 630 (Allergan-Humphrey), using the 30-2 threshold test with evaluation by software provided by the manufacturer (STATPAC; Allergan-Humphrey). All patients were experienced in automated threshold perimetry, and results were analyzed beginning with the second visual field examination. To be considered reproducible, either at the study entry or during the follow-up, individual field defects had to be confirmed in at least two separate testing sessions performed within 5 days. In each patient, sensitivity loss at a given location was confirmed within ±2 dB. The locations of defects (Table 1) were confirmed within ±6°. Intratest perimetric reliability was evaluated as fixation losses and false-positive and false-negative errors, according to Bickler-Bluth et al. Short-term fluctuation (SF) did not exceed the 2% range in each patient. When outside the normal range, SF depended on the individual degree of visual loss.

For data analysis, the global field sensitivity indices mean deviation (MD) and pattern SD (PSD) were used, and sectorial mean perimetric deviation was also calculated from the total-deviation plot, according to the method proposed by Kono et al. (Fig. 1). More specifically, the Humphrey visual field was divided into four sectors (central, temporal, superior, and inferior) corresponding to the different quadrants of the HRT disc rim (temporal, nasal, inferior, and superior, respectively). This correspondence was related to the anatomic course of retinal nerve fibers to the optic disc. Visual field loss of the patients ranged from minimal to a marked degree, according to the scheme proposed by Wall and George.

### Table 1. Demographic and Clinical Features of Patients

<table>
<thead>
<tr>
<th>Patient/Age (y)/Sex</th>
<th>Symptoms at Baseline</th>
<th>Duration of Symptoms at Baseline (mo)</th>
<th>Visual Field Type of Defect at Baseline</th>
<th>Follow-up Duration (mo)</th>
<th>Test Schedule (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/20/F</td>
<td>TVO</td>
<td>2</td>
<td>IN G</td>
<td>14.5</td>
<td>0, 1.5, 2.5, 3, 5, 14.5</td>
</tr>
<tr>
<td>2/44/M</td>
<td>TVO, diplopia</td>
<td>6</td>
<td>G G</td>
<td>5</td>
<td>0, 0.5, 0.65, 0.8, 1, 1.5, 5</td>
</tr>
<tr>
<td>3/33/F</td>
<td>TVO, photopsia</td>
<td>4</td>
<td>BSE, IN BSE, IN</td>
<td>28.5</td>
<td>0, 3.5, 10, 12.5, 23, 28.5</td>
</tr>
<tr>
<td>4/58/M</td>
<td>Diplopia</td>
<td>3</td>
<td>C IN</td>
<td>19</td>
<td>0, 1.5, 4.5, 11, 19</td>
</tr>
<tr>
<td>5/39/M</td>
<td>TVO, photopsia</td>
<td>6</td>
<td>BSE</td>
<td>9</td>
<td>0, 1, 9</td>
</tr>
<tr>
<td>6/47/F</td>
<td>TVO, photopsia</td>
<td>2</td>
<td>G G</td>
<td>10.5</td>
<td>0, 1.5, 2.5, 4, 10.5</td>
</tr>
<tr>
<td>7/54/F</td>
<td>TVO</td>
<td>4</td>
<td>BSE, BSE N</td>
<td>30</td>
<td>0, 3, 9.5, 20, 30</td>
</tr>
<tr>
<td>8/34/M</td>
<td>TVO, photopsia, diplopia</td>
<td>1</td>
<td>G C</td>
<td>20</td>
<td>0, 1, 1.5, 2.5, 4, 7, 14, 20</td>
</tr>
</tbody>
</table>

RE, right eye; LE, left eye; TVO, transient visual obscurations; BSE, blind-spot enlargement; C, concentric reduction; G, generalized depression; IN, inferonasal defect; N, nasal defect, —, no defect.

* 30-2 threshold test.
RESULTS

Cross-sectional Analysis

Individual tomographic and perimetric data, derived from global analysis at baseline, are reported in Table 2. Some patients had a considerable degree of asymmetric papilledema (e.g., patients 1 and 7), as expressed by tomographic parameters, whereas in the remaining six, the degree of disc edema was similar in both eyes. Perimetric sensitivity losses expressed by MD and PSD tended to be systematically larger in eyes with a greater amount of disc edema. There were significant negative correlations between the individual tomographic values and the corresponding perimetric MDs obtained at baseline, either in the global or sectorial analysis (Spearman’s $r \leq -0.62$). Correlations between the tomographic values and the perimetric PSD did not attain statistical significance, even though the trend was similar to that observed for the MD.

Scatterplots of the individual Humphrey MD values as a function of the corresponding tomographic VAR and VAS parameters are shown in Figure 2. Data obtained from global analysis and from the analysis of temporal and inferior disc sectors are reported. Linear regression lines are fitted to the data points. MD losses tended to be progressively greater in eyes with greater HRT values. In the temporal and inferior sectors, a topographic relationship between tomographic disc elevation and perimetric loss was observed. Correlations between volumetric and perimetric values at nasal and superior disc sectors also showed the same trend. The correlational analysis was performed again after excluding all the peripapillary locations (10 points adjacent to the blind-spot projection), to minimize the possible artifacts due to blind-spot enlargement.\textsuperscript{8,9} This new analysis (not shown in the Figure) provided very similar results.

Most correlations recorded at baseline between interocular tomographic and perimetric differences (MD and PSD), for use in either global and sectorial analysis, were significant at $P \leq 0.05$ (Spearman’s $r \leq -0.57$ for MD, $r \geq 0.64$ for PSD). Scatterplots of the individual intereye Humphrey MD difference values, plotted as a function of the corresponding volumetric differences are shown in Figure 3. Data collected from the global analysis and from the analysis of the inferior disc

### Table 2. Morphometric and Perimetric Data from Patients at Baseline

<table>
<thead>
<tr>
<th>Patient</th>
<th>VAR (mm$^3$)</th>
<th>VAS (mm$^3$)</th>
<th>EMH (mm)</th>
<th>MxHC (mm)</th>
<th>MD (dB)</th>
<th>PSD (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RE LE</td>
<td>RE LE</td>
<td>RE LE</td>
<td>RE LE</td>
<td>RE LE</td>
<td>RE LE</td>
</tr>
<tr>
<td>1</td>
<td>3.29 (0.36)</td>
<td>14.41 (0.85)</td>
<td>5.02 (0.31)</td>
<td>0.28 (0.02)</td>
<td>0.71 (0.04)</td>
<td>-4.23 (0.02)</td>
</tr>
<tr>
<td>2</td>
<td>16.49 (0.35)</td>
<td>16.51 (0.62)</td>
<td>15.22 (0.19)</td>
<td>0.79 (0.01)</td>
<td>1.46 (0.01)</td>
<td>-12.84 (0.05)</td>
</tr>
<tr>
<td>3</td>
<td>6.73 (0.35)</td>
<td>8.04 (0.16)</td>
<td>6.47 (0.28)</td>
<td>0.36 (0.02)</td>
<td>0.98 (0.02)</td>
<td>-4.92 (0.02)</td>
</tr>
<tr>
<td>4</td>
<td>6.03 (0.24)</td>
<td>4.24 (0.90)</td>
<td>5.62 (0.08)</td>
<td>0.35 (0.01)</td>
<td>1.02 (0.01)</td>
<td>-4.43 (0.04)</td>
</tr>
<tr>
<td>5</td>
<td>9.66 (0.07)</td>
<td>7.86 (0.17)</td>
<td>7.55 (0.04)</td>
<td>0.40 (0.01)</td>
<td>1.05 (0.02)</td>
<td>-3.58 (0.05)</td>
</tr>
<tr>
<td>6</td>
<td>12.61 (0.34)</td>
<td>15.31 (0.19)</td>
<td>9.21 (0.04)</td>
<td>0.50 (0.01)</td>
<td>1.06 (0.01)</td>
<td>-7.41 (0.01)</td>
</tr>
<tr>
<td>7</td>
<td>2.48 (0.27)</td>
<td>9.92 (0.99)</td>
<td>3.68 (0.05)</td>
<td>0.24 (0.01)</td>
<td>0.74 (0.01)</td>
<td>-1.34 (0.02)</td>
</tr>
<tr>
<td>8</td>
<td>17.13 (0.57)</td>
<td>15.19 (0.7)</td>
<td>11.09 (0.1)</td>
<td>0.57 (0.01)</td>
<td>1.21 (0.01)</td>
<td>-15.28 (0.03)</td>
</tr>
</tbody>
</table>

Data represent means with SDs in parentheses. VAR, volume above reference; VAS, volume above surface; EMH, effective mean height; MxHC, maximum height in contour; MD, perimetric mean deviation; PSD, perimetric pattern standard deviation; RE, right eye; LE, left eye.

* SD of the measurements from three consecutive 20° images.
Negative values of volumetric differences indicate that left eye discs were more edematous than right ones. Similarly, for MD differences, positive values indicate that left eyes were more functionally damaged than right ones. It is apparent from scatterplots of Figure 3 that interocular tomographic differences were associated in both entity and direction to the corresponding perimetric differences.

**Longitudinal Analysis**

In Figure 4, examples of HRT reflectance images obtained at baseline and at different times during the follow-up from the right eye of a patient with papilledema from IIH (patient 1; Table 1) are shown. Disc edema z-profiles, taken along vertical meridians (indicated by the thick lines) crossing both poles, are...
shown for each image. In the same figure, perimetric results of the tested eye, obtained at corresponding follow-up times, are also reported. The figure shows that during the follow-up period, there was a decrease of disc edema (as shown by the changes in the VAR and VAS values) that was paralleled by an improvement of visual field indices (MD and PSD).

Figure 5 shows the tomographic VAS and perimetric MD individually recorded at various times over the follow-up period. Data are separately plotted for right and left eyes. After medical treatment, the VAS declined rapidly in most patients, indicating a trend toward regression of disc edema.

In parallel with the decline in the VAS, perimetric MD tended to move toward normal values at comparable follow-up times.

Box plots of volumetric and perimetric values recorded from the right eyes of patients at baseline and after approximately 3 months of follow-up are shown in Figure 6. A Wilcoxon sign test showed that volumetric values significantly decreased (VAR, z-score: -2.28, \( P = 0.017 \); VAS, z-score: -2.52, \( P = 0.012 \)), whereas perimetric MD increased (z-score: 2.24, \( P = 0.025 \)) at comparable follow-up times. Perimetric PSD changes were not statistically significant.
DISCUSSION

Studies evaluating the correlation between degree of papilledema and visual field loss have reported different and, at least in part, conflicting results (see Table 3). Although a qualitative correlation between high-grade papilledema and perimetric loss has been found by some investigators, it has been suggested that the severity of visual field loss in individual patients cannot be predicted from the severity of papilledema. Göbel et al. did not find any quantitative correlation between HRT measurements of disc swelling and automated field sensitivity. More recently, Mulholland et al. reported that, in individual patients with IIH, changes in CSLO disc volume were qualitatively correlated with corresponding perimetric sensitivity changes in the short term. However, no quantitative correlations were reported, either in cross-sectional or longitudinal measurements. Wall and White, evaluating patients with IIH who had asymmetric papilledema, found a significant correlation between visual field sensitivity loss and papilledema grade, evaluated on optic disc photographs according to the Frisén scheme. The strength of the correlation was partially weakened by a large interindividual variability, so that r was much greater when the fellow eyes of several patients were compared. In the present study, correlations between morphometric CSLO parameters and perimetric indices MD and PSD were evaluated either cross-sectionally or longitudinally in a group of patients with recently diagnosed papilledema associated with IIH. This sample of patients, because it was equally distributed between males and females, may not be representative of IIH, a disease more prevalent in females. However, the purpose of this study was to analyze these correlations in papilledema and not in IIH. In addition, the patients included in the study

<table>
<thead>
<tr>
<th>Studies</th>
<th>Visual Function and Papilledema Assessment</th>
<th>Reported Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rush</td>
<td>VA, VF by Aimark or Goldmann perimeter and tangent screen; ophthalmoscopy.</td>
<td>No significant correlation</td>
</tr>
<tr>
<td>Orcutt</td>
<td>Corrected Snellen VA, VF by Goldmann perimeter and tangent screen; ophthalmoscopy and fundus photography.</td>
<td>Qualitative correlation in atrophic or high-grade papilledema</td>
</tr>
<tr>
<td>Smith and Baker</td>
<td>Best corrected VA, VF by Goldmann, Digilab (full-field thresholding program), and Octopus (32 program; Interzeig, Switzerland) perimeters; stereoscopic fundus photography.</td>
<td>Qualitative correlation in higher grades of papilledema</td>
</tr>
<tr>
<td>Corbett</td>
<td>Snellen VA, VF; optic disc photography.</td>
<td>No significant correlation</td>
</tr>
<tr>
<td>Wall and George</td>
<td>Best corrected Snellen VA, VF by Goldmann, Octopus 201 and Humphrey perimeters (full-field or central 30° automated strategy); ophthalmoscopy and stereoscopic fundus photography.</td>
<td>Qualitative correlation in high grades of papilledema</td>
</tr>
<tr>
<td>Göbel et al.</td>
<td>VA, VF by Goldmann, Octopus 201 and 500 perimeters; fundus photography, and confocal tomography by HRT (MxHC and VAS parameters considered).</td>
<td>No significant correlations</td>
</tr>
<tr>
<td>Mulholland et al.</td>
<td>Best refracted Snellen VA, VF by Goldmann and Humphrey perimeters (automated 30-2 threshold test); stereoscopic optic disc assessment, stereo disc photography, and confocal tomography by HRT (VAS parameter considered).</td>
<td>No significant correlation</td>
</tr>
<tr>
<td>Wall and White</td>
<td>Best corrected VA, conventional automated perimetry (Humphrey 24-2 threshold test), high-pass resolution perimetry and motion perimetry; optic disc photography.</td>
<td>Qualitative correlation, notwithstanding a considerable interindividual variation</td>
</tr>
</tbody>
</table>

* Testing strategies not mentioned. VA, visual acuity; VF, visual field.
had reliable visual fields with a relatively high reproducibility of their defects. Test-retest variability of perimetric sensitivity usually represents a major concern when evaluating changes over time in patients with early field losses. The good reproducibility found in this patient sample allowed morphofunctional correlations to be evaluated with a low degree of noise.

The results showed that, at baseline evaluations, there was a significant negative correlation between the disc volume and height and the perimetric MD measurements. Intercorrelation analysis confirmed these findings and showed agreement with the data of Wall and White. The correlations showed a topographic specificity—that is, regional localized edema was associated with sensitivity losses at corresponding field sectors. As far as we know, this is the first report to evaluate such a topographic relationship in papilledema. In the follow-up period, the optic disc volumetric changes appeared to be accompanied by corresponding perimetric variations. In this study, patients with advanced disc-swelling phases were excluded, because irreversible axonal damage might hinder the correlation between disc morphology and perimetry.

The correlations between papilledema grade and functional losses, as well as the trends observed over the follow-up period, lend support to the hypothesis that both techniques can be used to monitor the amount of disc edema and the effectiveness of treatments aimed at reducing intracranial hypertension. In papilledema, perimetric loss is thought to result from elevated tissue pressure within the optic nerve due to the increased CSF pressure transmitted through optic nerve sheaths. Of the two types of field loss resulting from disc edema, the blind-spot enlargement and the nerve fiber–related visual field defects, the former is considered to be artifactual, being a consequence of edema-induced local hyperopia, photoreceptor misalignment, or both, whereas the latter are commonly accepted as the primary indication of damage to the axons of retinal ganglion cells.

It cannot be excluded that both types of defects may correlate with the amount of papilledema recorded in individual patients. However, a correlational analysis, performed on the patients’ right eyes after excluding thresholds measured at all the peripapillary locations, provided results very similar to those of the original analysis. In addition, there are reasons to suspect that a specific correlation between nerve fiber–related visual defects and the degree of edema may hold, at least in patients such as the one reported in Figure 4, in whom the right eye showed at baseline a typical inferonasal nerve fiber defect that could not have been ascribed to blind-spot enlargement. Significant improvement of the field defect in this patient was mirrored by a regression of edema in the topographically corresponding superior sector of the optic disc. Although this sectoral association supports the relationship of localized axonal damage with corresponding perimetric abnormalities, further studies on a large cohort of patients are needed to clarify this issue.

In this patient sample, CSLO assessment was always performed on 20° images, unlike the procedures used by Gobel et al. and Mulholland et al., thus providing a more homogeneous sample of data while minimizing artifactual values. Furthermore, analysis of volumetric measurements by using both VAS and VAR parameters may result in a more accurate estimate of the amount of disc edema, compared, for instance, with that reported by Mulholland et al. This is supported by two different pieces of evidence. First, the VAR reference plane is derived from only a very small (temporal 6°) portion of the contour line, which makes sense in glaucoma studies, but does not appear very meaningful for quantifying disc edema. Even small edematous retinal areas under the contour line in the temporal segment may largely underestimate the papilledema, especially for follow-up evaluations. By contrast, the use of the whole circumference to assess a reference surface (the HRT curved surface used for the VAS measurement) may compensate mild contour line height variations and minimize measurement errors. Second, the use of the VAS parameter was suggested by previous reports in which its accuracy and reproducibility were evaluated in the presence of retinal elevations.

In conclusion, in the present findings in recently diagnosed papilledema, morphometric abnormalities were quantitatively associated with perimetric threshold alterations. Reversibility of functional damage also appeared to occur in parallel with disc-swelling resolution. Taken together, the data further support the use of the HRT technique as a noninvasive, quantitative method of monitoring the amount and evolution of papilledema, as well as of evaluating the effects of treatments.

References