Follow-up of Mild Papilledema in Idiopathic Intracranial Hypertension with Optical Coherence Tomography

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PURPOSE. To evaluate optical coherence tomography (OCT) measurement of peripapillary retinal nerve fiber layer (RNFL) thickness in patients with mild papilledema associated with idiopathic intracranial hypertension.

METHODS. Patients with papilledema underwent a complete ophthalmic examination, including peripapillary RNFL analysis with OCT (Fast RNFL thickness 3.46; Carl Zeiss Meditec, Inc., Dublin, CA) at diagnosis and 3, 6, and 12 months after presentation. Age- and sex-matched control subjects underwent a similar evaluation. Changes in RNFL overall thickness and by quadrant and interocular differences were evaluated and studied regarding changes in visual field global indices (mean deviation [MD] and pattern standard deviation [PSD]).

RESULTS. Both eyes of 22 patients with mild papilledema and 22 control subjects were included. At diagnosis, the RNFL thickness was $183.3 \pm 74.6 \mu m$ and $74.9 \% (78.5 \mu m)$ greater than in control eyes. Mean RNFL thicknesses in all quadrants were significantly greater in eyes with papilledema ($P = 0.000$). The mean average RNFL was significantly correlated with the MD ($r = -0.451, P = 0.002$) and PSD ($r = 0.370, P = 0.013$) at diagnosis. The RNFL thickness decreased significantly ($P = 0.000$), whereas the mean MD and the mean PSD improved ($P = 0.000$ and $P = 0.005$, respectively) at each follow-up visit. Regression analysis showed that for every 10 $\mu m$ of mean RNFL thickness increase at baseline, there was a 0.6-dB decrease in MD at the last follow-up.

CONCLUSIONS. Peripapillary RNFL thickness abnormalities assessed by OCT in patients with mild papilledema were quantitatively correlated with visual field sensitivity losses. The data support the possible use of OCT as a noninvasive quantitative method of monitoring the amount and evolution of papilledema. (Invest Ophthalmol Vis Sci. 2009;50:5197–5200) DOI:10.1167/iovs.08-2528

Idiopathic intracranial hypertension, also known as pseudotumor cerebi, is characterized by elevated intracranial pressure, absent focal neurologic signs, and normal cerebrospinal fluid (CSF) composition. The main clinical complaints are headache and visual disturbances.1,2 The disease course is often lengthy, and therapy must be guided by clinical signs, the extent of papilledema, and the CSF opening pressure. Several approaches have been used to analyze the papilledema, either functionally or morphologically. The prominent role of automated perimeter in detecting functional losses and after progression has been emphasized.3,4 Morphologic techniques include ophthalmoscopic examination, optic disc and retinal nerve fiber layer (RNFL) photography, and echographic transverse optic nerve diameter measurements. Recently, the reliability of confocal scanning laser ophthalmoscopy (CSLO) has been reported to be a quantitative method of evaluating papilledema.3,5,6

Optical coherence tomography (OCT), a noninvasive imaging technique that obtains retinal images closely resembling histologic preparations, is useful for evaluating the peripapillary nerve fiber layer. OCT can detect and quantify diffuse thickening of the RNFL in eyes with optic disc edema associated with several neuropathies.8,9 In two recent studies, papilledema has been evaluated in children by OCT,10,11 but we found no prospective evaluations of papilledema by OCT in adults. The goals of this study were to report the findings of OCT evaluation in adults with papilledema associated with idiopathic intracranial hypertension at onset and for up to a 12-month follow-up and to assess whether the degree of disc swelling measured by OCT correlates quantitatively with the severity of visual dysfunction determined by automated perimetry.

METHODS

The study patients were recruited from larger cohorts of patients evaluated at the Neuro-Ophthalmology Department of our institution between September 1, 2005, and September 30, 2007. Consecutive patients older than 18 years with a recent clinical diagnosis of idiopathic intracranial hypertension based on the updated diagnostic criteria and mild papilledema were considered for this prospective study.1,2 All patients underwent magnetic resonance imaging with venography to exclude a diagnosis of venous sinus thrombosis.5,13 Exclusion criteria were the presence of an ocular disease other than papilledema, the presence of systemic diseases that precluded adequate follow-up and examination, and a refractive error greater than 5.0 D of spherical equivalent or 3.0 D of astigmatism in either eye. All participants provided informed consent. The study protocol adhered to the Declaration of Helsinki and was approved by the local ethics committee.

Both eyes of patients who met the study criteria underwent a complete ophthalmic evaluation including Snellen visual acuity (VA), biomicroscopy of the anterior and posterior segments, intraocular pressure measurement, automated perimetry (Swedish Interactive Threshold Algorithm standard 24-2 strategy, Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Dublin, CA), and OCT imaging. A 90-D lens biomicroscopic assessment of the degree of papilledema was based on the scheme proposed by Frisén.14 No patients had signs of atrophic papilledema.

OCT scanning was performed (Stratus OCT; Carl Zeiss Meditec) after pharmacologic mydriasis. Image acquisition was performed with the Fast RNFL Thickness (3.46) strategy. Satisfactory image quality was defined as good centration on the optic disc and a signal strength of 6 or greater. RNFL thicknesses were obtained with the built-in OCT software RNFL Thickness Average Analysis protocol. A color-coded
graph displays the RNFL measurements and compares them with the age-matched data of a normative database. Testing was repeated 3, 6, and 12 months after the diagnosis.

Age- and sex-matched control subjects were recruited from among workers at our center and the relatives of patients. Control subjects with no history or evidence of current ocular disease underwent the same OCT evaluation as did the patients.

The treatment regimen in these patients was primarily conservative, including acetazolamide (starting at a dose of 1 g/d, in divided doses of 250 mg four times daily and tapered down slowly) and a weight-reduction program, including a combination of diet and exercise, prescribed by a nutritionist. In two patients, a lumbar plexoneal shunt was performed.

Given the small sample size, for statistical analyses, nonparametric tests were used (SPSS 12.0, SPSS Inc., Chicago, IL). OCT and the perimetric results of each patient and the interocular differences of both OCT and perimetric values were included in the analysis. For data analyses, the global field sensitivity indices mean deviation (MD) and pattern standard deviation (PSD) were used. The Friedman test was used to compare repeated measurements of the variables. The Wilcoxon sign test for matched pairs was used to compare OCT and perimetric measures obtained at baseline and 1 year of treatment. The Mann–Whitney test was used for comparisons with control subjects. Correlations between OCT and perimetric data were evaluated by nonparametric Spearman’s correlation analysis. All statistical tests were two-tailed with the significance level set at 0.05.

## Results

Twenty-two patients were recruited (16 women and 6 men; median age, 40 years; range, 20–54). At the time of diagnosis, the median best corrected VA was 20/20 and the median optic nerve clinical grade was 2.0 (range, 1–5). All patients had bilateral edema. The median CSF opening pressure was 29 cm H$_2$O (range, 25.5–45).

Table 1 shows the mean peripapillary RNFL thickness measured by OCT in patients and control subjects at diagnosis. The mean average RNFL and RNFL thicknesses in all quadrants in the eyes with papilledema were significantly greater than that of control subjects ($P = 0.000$).

The mean initial RNFL thickness represented a mean increase in RNFL thickness of 74.9% (78.5 μm) compared with the RNFL thickness of the control eyes. The percentages of RNFL increases in the superior, inferior, nasal, and temporal quadrants were 55.1%, 73.8%, 84.8%, and 81.2%, respectively, compared with the control eyes.

At presentation, 32 eyes (72.7%) had a mean average RNFL thickness classified by the OCT normalized database as higher than normal; the 12 eyes with a mean RNFL thickness classified as normal had at least one quadrant in which it was higher than normal. Only one patient, having at diagnosis a CSF opening pressure of 35 cm H$_2$O, had a mean average RNFL thickness classified as normal in both eyes; however, in both eyes sectorial edema was identified. An enlargement of the blind spot was also present in both eyes.

At diagnosis, the peripapillary RNFL was thickened in a median of seven clock hour sectors (range, 2–12) above the upper 95% confidence interval limit of normal. The median number of quadrants with values higher than expected was 2.5 (range, 1–4). According to a normalized database, 34 (77.3%), 28 (63.6%), 28 (63.6%), and 24 (54.5%) eyes had RNFL thicknesses considered higher than normal at baseline superiorly, inferiorly, nasally, and temporally, respectively.

Although nonsignificant, the mean average RNFL thickness was higher in left eyes than in right eyes ($P = 0.827$). The mean MD and mean PSD were worse in the left eyes than in the right eyes ($P = 0.971$ and $P = 0.296$, respectively; Table 2).

The most common visual field defects at presentation were enlargement of the blind spot (22 eyes, 50%) and diffuse visual field loss (16 eyes, 36.4%). The mean MD and mean PSD at diagnosis were $-6.2 \pm 7.6$ and $4.3 \pm 2.4$, respectively.

The mean initial average RNFL was significantly correlated with the initial MD ($\alpha = -0.451, P = 0.002$) and PSD ($\alpha = 0.370, P = 0.013$). There was neither correlation between the mean CSF opening pressure and the initial average RNFL thickness ($P = 0.108$) nor between the calculated CSF pressure and intraocular pressure ratio and the initial average RNFL thickness ($P = 0.000$).

The mean RNFL thickness and visual field indices at each visit are shown in Table 3. The mean average RNFL at the 1-year visit was significantly lower than that at diagnosis ($P = 0.000$). Statistical analysis of the evolution of the mean average RNFL thicknesses showed a significant decrease at each visit ($P = 0.000$). The median VA remained stable.

At the 1-year follow-up visit, the mean average RNFL thicknesses were classified as normal in 40 (90.9%) eyes and below normal in 4 eyes ($P < 5\%$).

At that time, the value in at least one quadrant in 14 (31.8%) eyes was significantly higher than the normal database, and the

## Table 1. Mean Peripapillary RNFL Thickness in Papilledema and Control Eyes at Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Papilledema Eyes (μm)</th>
<th>Control Eyes (μm)</th>
<th>Mean Difference</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>183.3 ± 74.7</td>
<td>104.8 ± 14.2</td>
<td>78.5 ± 11.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Superior</td>
<td>210 ± 83.5</td>
<td>135.3 ± 13.4</td>
<td>74.6 ± 15.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Inferior</td>
<td>226.3 ± 88.3</td>
<td>130.2 ± 23.7</td>
<td>96.1 ± 16.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Nasal</td>
<td>146 ± 72.4</td>
<td>79 ± 14.3</td>
<td>67 ± 13.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Temporal</td>
<td>150.6 ± 111</td>
<td>83.1 ± 36.4</td>
<td>67.5 ± 20.7</td>
<td>0.000</td>
</tr>
</tbody>
</table>

## Table 2. OCT and Perimetric Data from Right and Left Eyes

<table>
<thead>
<tr>
<th></th>
<th>Right eye</th>
<th>Left eye</th>
<th>Mean Difference</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average RNFL</td>
<td>180.7 ± 75.5</td>
<td>186 ± 75.7</td>
<td>99.9 ± 25</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean difference</td>
<td>$-5.3 \pm 23.1$</td>
<td>14.2 ± 9.1</td>
<td>0.827</td>
<td>0.511</td>
</tr>
<tr>
<td>Mean MD</td>
<td>1.3 ± 2.3</td>
<td>3.2 ± 2.4</td>
<td>0.971</td>
<td>0.716</td>
</tr>
<tr>
<td>Mean PSD</td>
<td>4 ± 2.2</td>
<td>4.7 ± 2.6</td>
<td>0.296</td>
<td>0.408</td>
</tr>
</tbody>
</table>

$^*$ Wilcoxon test.

† Mann–Whitney test.
value in at least one quadrant in 10 (22.7%) eyes was classified as thinner than normal.

At the 1-year follow-up visit, 29 (66%) eyes had normal visual fields, 8 (18%) eyes had enlargement of the blind spot and 7 (16%) eyes had irreversible visual field loss. In the 10 eyes in which the final RNFL measurements were classified as thinner than normal by OCT, we found that 3 eyes had a visual field constriction, 3 had defects in the inferonasal quadrant, and 1 had scotomas in the superior arcuate area. All eyes that had irreversible visual field loss had at least one quadrant classified as significantly thinner than normal in OCT. The three eyes having a visual field constriction had an average RNFL thinning classified as below normal.

At the 1-year-visit, there was no significant difference in the mean average RNFL between papilledema and control eyes ($P = 0.268$). The mean MD and PSD significantly improved at each follow-up visit ($P = 0.000$ and $P = 0.005$, respectively).

At the 1-year follow-up visit, the mean average RNFL thickness at diagnosis was inversely correlated with the MD ($\alpha = -0.596$, $P = 0.000$) and directly with PSD ($\alpha = 0.487$, $P = 0.03$). Regression analysis indicated a 0.6-dB worsening in MD per 10-μm increase in mean RNFL thickness at baseline. The mean average RNFL was thinner in left eyes compared with right eyes ($P = 0.511$) and the mean MD was worse ($P = 0.716$; Table 2).

### DISCUSSION

Idiopathic intracranial hypertension is a relatively uncommon disorder with an average annual incidence of about one to two cases per 100,000 people in the general population. Obesity and being female are the most frequently encountered risk factors. Several studies have shown that quantitative perimetry and optic nerve examination are more sensitive than VA. The presence of papilledema is the hallmark of suspected disease, and its severity determines the overall treatment strategy. Papilledema can be monitored using quantitative and qualitative methods.

Results in studies in which a correlation between the degree of papilledema and visual field loss were evaluated are contradictory. Some investigators have reported a qualitative correlation between papilledema and perimetric loss. Wall and White, who evaluated patients with idiopathic intracranial hypertension and asymmetric papilledema, reported a significant correlation between visual field sensitivity loss and papilledema grade, after assessing optic disc photographs.

CSLO has been used successfully to detect changes in optic disc volume during the course of the idiopathic intracranial hypertension disease process. Göbel et al. did not find a quantitative correlation between Heidelberg Retinal Tomograph (Heidelberg Engineering, Heidelberg, Germany) measurements of disc swelling and automated field sensitivity. More recently, Salgarello et al. reported that the therapeutic improvement of the volumetric parameters in CSLO may parallel the recovery of perimetric sensitivity. Few data have been published on adults and children with OCT evaluation for pseudotumor cerebri.

In the present study, we evaluated the correlations between the RNFL thickness measured by OCT and the perimetric indices MD and PSD in patients with mild papilledema associated with idiopathic intracranial hypertension over a 1-year follow-up. To our knowledge, this is the first report to evaluate such a relationship in adults with papilledema using OCT.

In the present study, OCT showed a greater average RNFL thickness in all four quadrants in eyes with papilledema compared with controls ($P = 0.000$). El-Dairi et al. reported a thicker average RNFL in eyes of children with pseudotumor cerebri compared with controls, but the RNFL differences were not significant in all quadrants probably because of the small sample size. The mean average RNFL thickness reported by EL-Dairi et al. (125.7 ± 29.6 μm) was lower than that in the present study (183.3 ± 74.7 μm) probably because of milder baseline optic disc edema (the median optic nerve clinical grade reported by them was 1.0 vs. 2.0 in the present study). Moreover, they did not report longitudinal data.

At baseline, we found a significant negative correlation between the mean average RNFL thickness and perimetric MD measurements ($\alpha = -0.451$, $P = 0.002$). In papilledema, perimetric loss may result from elevated tissue pressure within the optic nerve due to the increased CSF pressure transmitted through the optic nerve sheaths. Unsurprisingly, perimetric sensitivity losses tended to be greater in eyes with more edema. Interocular analysis confirmed these findings and showed agreement with the data published by Salgarello et al. who used CSLO (Table 2).

We did not evaluate patients with advanced disc swelling, because irreversible axonal damage could hinder a correlation between disc morphology and perimetry.

After treatment, the mean RNFL thickness declined rapidly, indicating a trend toward regression of disc edema ($P = 0.000$). At the 3-month visit, the RNFL thickness decreased 31.9% compared with baseline. During the follow-up period, the peripapillary optic disc changes in OCT appeared to be accompanied by corresponding perimetric variations in most patients. Similarly, Salgarello et al. studied eight patients with idiopathic intracranial hypertension and reported that CSLO disc volume changes correlated with corresponding perimetric threshold alterations, and resolution of the papilledema coincided with improved visual field defects. Our findings in the present study strongly support these observations.

At the 1-year follow-up, the mean average RNFL thickness was classified as normal in 90.9% of eyes. At that time, the MD correlated inversely with the mean average RNFL thickness at diagnosis ($\alpha = -0.596$, $P = 0.000$); in fact, we found a 0.6-dB loss in MD for every 10-μm increase in the overall RNFL thickness.

The main problem using OCT to observe patients with papilledema, is there is no way, based on OCT alone, to determine, when RNFL thickness returns toward normal,
whether it implies patients are improving or that they are actually losing nerve fibers.

Sometimes when optic disc edema resolves, axonal damage has already occurred but cannot yet be detected anatomically. At this time, a discrepancy between OCT and visual field testing can be helpful. In fact, in the present study, all three eyes that developed irreversible visual field constriction, improved initially in OCT but not in visual field testing; indicating that at least in these three cases, RNFL attrition and swelling could occur at the same time. The tempo of visual loss may be rapid or slowly progressive, and so it is necessary to wait until the RNFL loss has reached a plateau to establish by OCT that irreversible damage has occurred.

In the present study, at the 1-year follow-up visit, the value in at least one quadrant was significantly higher than that in the normal database in 14 (31.8%) eyes, and 8 (18.2%) eyes had enlargement of the blind spot. A longer follow-up is necessary to determine whether these eyes will have irreversible RNFL damage.

The correlations between papilledema grade and functional losses and the trends observed over the follow-up period support the use of both techniques, OCT and perimeter, for monitoring the amount of disc edema and the effectiveness of treatments to reduce intracranial hypertension.

A limitation of the present study was the small number of eyes; however, idiopathic intracranial hypertension is a relatively rare clinical entity, and a large number of cases is difficult to collect at one site. In the present study, mostly patients had mild papilledema in the early course of their disease with a benign clinical course. Most visual defects associated with papilledema are reversible if intracranial pressure is lowered before there is optic nerve damage. In fact, approximately two thirds of patients included in this study did not show evidence of permanent nerve fiber damage at 1 year of follow-up. Our results cannot be extrapolated to more advanced papilledema.

In addition, the follow-up time was short. At the 1-year visit, 31.8% of the eyes had an RNFL thickness that was higher in at least one quadrant compared with that of the normal database, indicating unresolved optic disc edema. Although we expected these percentages to change with longer follow-up, our data support that over 12 months, the improvement in automated perimeter and the changes in OCT measurements correlated significantly.

The present study showed that RNFL thickness abnormalities evaluated by OCT in mild papilledema are quantitatively associated with perimetric threshold alterations at baseline and over a 1-year follow-up period. Therapeutic improvement of these parameters is accompanied by recovery in visual field indices. Perimetric sensitivity loss tended to be greater in eyes with more edema.

To differentiate RNFL attrition versus improvement in RNFL swelling based on OCT alone, it is necessary to extend follow-up time and to repeat OCT until a plateau can be firmly established.

These data support the use of OCT as a noninvasive, quantitative method of monitoring the amount and the evolution of papilledema and the treatment effects.

References