The Effect of Treatment of Idiopathic Intracranial Hypertension on Prevalence of Retinal and Choroidal Folds

MARK J. KUPERSMITH, PATRICK A. SIBONY, STEVEN E. FELDON, JUI-KAI WANG, MONA GARVIN, AND RANDY KARDON, THE OCT SUB-STUDY GROUP FOR THE NORDIC IDIOPATHIC INTRACRANIAL HYPERTENSION TREATMENT TRIAL

PURPOSE: We described 3 types of folds in the retina and a crease in the outer retina associated with papilledema owing to idiopathic intracranial hypertension (IIH) at presentation. We report the change in folds relative to treatment of IIH over the 6 months.

METHODS: In this substudy of a randomized clinical trial, study eyes of subjects assigned to acetazolamide (ACZ, n = 44) or placebo (PLB, n = 43) had spectral-domain optical coherence tomography (SDOCT) images of the optic disc and macula regions at baseline and at 3 and 6 months. Images were evaluated for peripapillary wrinkles (PPW), retinal folds (RF), choroidal folds (CF), and creases using transaxial and en face views. The optic nerve head (ONH) shape, retinal nerve fiber layer (RNFL) thickness, ONH volume, and papilledema grade were measured. Outcome was determination of the presence or absence of PPW, RF, CF, and creases.

RESULTS: At presentation, except for an increase of PPW in ACZ eyes (64% vs 28%), both treatment groups were matched for all OCT features. At 6 months, ACZ-treated, but not PLB-treated, eyes had fewer folds of all types (P < .01), with a 57% reduction in frequency of RF. Creases did not resolve. Resolution of RF, but not of PPW and CF, was associated with significant reduction in RNFL thickness, ONH volume, and papilledema grade.

CONCLUSIONS: The various types of retinal folds associated with papilledema reflect biodynamic processes and show an ACZ treatment effect. Persistence of these folds despite marked improvement in ONH swelling suggests permanent changes in the affected retinal tissues. (Am J Ophthalmol 2017;176:77–86. © 2016 Elsevier Inc. All rights reserved.)

THE OPTICAL COHERENCE TOMOGRAPHY (OCT) substudy of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) described several types of retinal and choroidal folds in patients with papilledema owing to idiopathic intracranial hypertension (IIH) with mild vision loss prior to treatment at presentation.1

The most common were (1) concentric or spiral peripapillary wrinkles (PPW) located in the retinal nerve fiber layer (RNFL), (2) horizontal or radial retinal folds (RF) in the inner and middle layers that spared the choroid, and (3) peripapillary outer retinal folds and creases. The least common were choroidal folds (CF) beneath the retinal pigment epithelial layer usually associated with overlying retinal folds. Each type of fold appeared to be related to specific features of IIH, including the amount of papilledema seen via OCT and the cerebrospinal fluid pressure (CSFp).

Spectral-domain (SD) OCT demonstrated folds of all types significantly better than high-quality stereophotographs of the optic disc and macula. The presence of folds did not correlate with visual acuity or perimetric mean deviation (MD) at baseline; however, this cohort only included patients with mild vision loss.2

The goal of this report is to describe the changes in the retinal and choroidal folds owing to IIH with and without treatment over 6 months. We also determined if the presence of folds correlated with changes in the degree of papilledema, the optic nerve head (ONH) neural canal border retinal pigment epithelium (RPE)/Bruch membrane (BM) displacement, and CSFp. Given the findings at baseline, we hypothesized that (1) fewer PPW, RF, and CF would be seen with reduction in the Frisén grade, mean RNFL thickness, and ONH volume over time; and (2) reduced CSFp would be associated with fewer choroidal and retinal folds.

METHODS

WE EVALUATED 87 STUDY SUBJECTS OF THE 125 ENROLLED IN THE OCT substudy of the IIHTT who had adequate OCT
scans to evaluate the various folds at all visits during a 6-month treatment interval (trial registration: clinicaltrials.gov identifier NCT01003639; registered October 28, 2009). The IIHTT study design, patient selection, clinical profiles, and outcome have been published elsewhere.2–4 Briefly, newly diagnosed, untreated patients with IIH who had an MD of −2.00 to −7.00 dB (Humphrey Field Analyzer II, SITA standard 24-2 test pattern; Carl Zeiss Meditec, Inc, Dublin, California, USA) in the worse eye (“study eye”) were enrolled. Participants were randomly assigned to receive a supervised diet and either acetazolamide (ACZ) or matching placebo (PLB) with escalating study drug dosage. Standardized fundus photographs, Frisén grading of photographs, best-corrected high- and low-contrast visual acuity, threshold 24-2 perimetry, CSFp, refractive error, and SDOCT imaging (using Cirrus 4000 SDOCT, 6.01 software; Carl Zeiss Meditec, Inc) were obtained on each patient during each visit. Institutional review boards from each participating site approved the study. The entire study was also approved by the St. Luke’s Roosevelt (now Mount Sinai West) Hospital Institutional Review Board, the institution of NORDIC Headquarters. The study complied with the Declaration of Helsinki. We selected month 6 for analysis for correlating change because (1) this was the IIHTT study outcome time point, with a strict protocol-controlled therapeutic intervention; and (2) there was a CSFp measurement obtained at 6 months for correlation. We used photographs and OCT images up to the 12 months to demonstrate some key points.

All study sites followed a specific protocol for photographs and SDOCT image collection. Stereo pair fundus photographs centered on the optic disc and macula were obtained from each site using a minimum of a 3-megapixel fundus camera capable of imaging a 30- to 35-degree field of view taken through a dilated pupil and submitted to the photographic reading center located at the University of Rochester for quality control and Frisén grading.5

Three standard SDOCT scans were used to image study eyes: (1) a 9-mm horizontal high-definition (HD) 5-line raster scan at 0.5-mm intervals across the central surface of the optic disc, (2) 2 ONH-centered volume scans, and (3) 2 macula-centered volume scans. OCT images were reviewed for quality control by the reading center at the University of California, Davis.6,7 Images were evaluated for folds using the 5-line raster and macula and optic nerve volume scans. Volume scans were also used for en face imaging with the Advanced Visualization Analysis program for the Cirrus SDOCT to view the retina at the internal limiting membrane, middle layers, and outer retina/RPE levels for each type of fold. Study eye images were evaluated by evaluators masked to the baseline results and treatment group assignment.

We used the features for each type of fold previously defined and used in the analysis of the baseline results.7 Briefly, PPW are closely spaced circumferential undulations on the disc surface or within half a disc diameter in the RNFL. RF are periodic surface or intraretinal radial or horizontal undulations greater than half a disc diameter from the disc. We restricted the diagnosis of CF to those eyes with undulations in the RPE/SM layer on the raster images and outer retinal or choroidal en face images. CF were almost always associated with overlying retinal folds. In a subsequent report we described peripapillary outer retinal folds characterized by undulations usually associated with outer retinal fluid or deeply furrowed “creases,” which appear to involve the ellipsoid zone to the outer nuclear layer.8 By ophthalmoscopy, the creases correspond to what is commonly called “high-water marks.”9 The current report also describes what occurs to these creases over the same 6-month interval.

We examined the association between folds and structural and functional parameters used in the IIHTT as outcome measures. Structural parameters included Frisén grade, total optic disc volume (mm³), mean RNFL thickness (μm), and the amount of shape deformation of the peripapillary RPE/SM layer toward the vitreous (eigenvalue of the second principal component; negative values were for deformations towards the vitreous and positive values for deformations away from the vitreous). Functional parameters included the number of correctly identified high- and low-contrast (2.5%) visual acuity letters and the perimetric MD. The methodology used to acquire and analyze each of the OCT parameters is fully described in the main outcome study for both the clinical trial and the OCT substudy.1,6,10

For the purpose of analysis we considered PPW, RF, and CF as present or absent. Folds were considered better if they resolved, had no change if they were demonstrated at presentation and follow-up, or were new folds if not present at baseline and were seen at either the 3- or 6-month evaluations.

IBM SPSS statistical software version 23 (IBM, Inc, Armonk, NY) was used for biostatistical evaluation of the data.11 The McNemar test was used to test significance for follow-up examination frequency of PPW, RF, and CF in each treatment group. The 2-sided Fisher exact test was used to test significance between treatment groups for PPW, RF, and CF. Analysis of variance (ANOVA) was used to compare the change in RNFL, ONH volume, ONH shape deformation, Frisén grade, CSFp (performed only at baseline and at 6 months), and the change in PPW, RF, or CF, which were resolved, unchanged, or newly developed. A post hoc Bonferroni alpha of 0.05 was used to adjust for the multiple features tested for each type of fold. Nonparametric correlations were made between the presence or absence of each type of fold and RNFL thickness, ONH volume, ONH shape deformation, Frisén grade, high- and low-contrast visual acuity, and MD. Given the low prevalence of creases, we only report the observed change over time.
TABLE 1. Frequency by Type of Fold at 3 and 6 Months in Treated and Placebo Groups

<table>
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<tr>
<th></th>
<th>ACZ (N = 44)</th>
<th>Placebo (N = 43)</th>
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<tbody>
<tr>
<td>Peripapillary wrinkles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
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<td>12 (27.9%)</td>
</tr>
<tr>
<td>3 months</td>
<td>28 (63.6%)</td>
<td>15 (34.9%)</td>
</tr>
<tr>
<td>6 months</td>
<td>24 (54.5%)</td>
<td>17 (39.5%)</td>
</tr>
<tr>
<td>Retinal folds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21 (47.7%)</td>
<td>23 (53.5%)</td>
</tr>
<tr>
<td>3 months</td>
<td>12 (27.3%)</td>
<td>22 (51.2%)</td>
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<tr>
<td>6 months</td>
<td>9 (20.5%)</td>
<td>22 (51.2%)</td>
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<tr>
<td>Choroidal folds</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7 (15.9%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>3 months</td>
<td>3 (6.8%)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>6 months</td>
<td>3 (3.8%)</td>
<td>2 (2.7%)</td>
</tr>
</tbody>
</table>

ACZ = acetazolamide.
Values are numbers (%) of eyes.
Comparison between ACZ and Placebo groups: *P = .001; **P = .007; ***P = .019; ****P = .003.
Change from baseline for ACZ group: *P = .001; †P = .032.
No other values significant difference between treatment groups or change over time.

RESULTS

THERE WERE 44 SUBJECTS IN THE ACZ-TREATED GROUP AND 43 subjects in the placebo-treated group. At presentation, study eyes in both treatment groups had similar Frisén grade, RNFL, ONH volume, and optic nerve shape, and similar frequencies for RF and CF. However, PPW were seen more frequently (in 35 eyes, 79.5%) in the ACZ group, compared with only 15 eyes (34.9%) in the placebo group (P = .001). Creases affected 3 eyes in the ACZ group and 6 eyes in the placebo group at baseline. The folds affected the macular region in 16 eyes (37%) in the placebo group and in 12 eyes (27%) in the ACZ group at baseline.

As previously reported in the entire substudy cohort, the increased average RNFL (279 ± 165 μm) and ONH volume (16.5 ± 3.8 mm³) at baseline were reduced for all study eyes at 3 months (169 ± 122 μm and 13.7 ± 3.1 mm³) and further decreased at 6 months (139 ± 85 μm and 12.7 ± 2.3 mm³). The baseline anterior displacement (toward the vitreous) ONH shape (−0.29 ± 1.07) normalized in the posterior direction (away from the vitreous) at 3 months (0.043 ± 0.91) and 6 months (0.27 ± 1.19). The ACZ-treated group was significantly improved for all 3 OCT measures compared with the placebo group.11 Also, as previously reported, the ACZ-treated group had greater reduction in CSFp at 6 months, but 15 subjects in the ACZ group as well as 25 placebo-treated subjects had 6-month opening pressure elevation above 25 cm H2O at 6 months, which we considered abnormal.

The frequency of all 3 types of folds changed at 3 and 6 months (Table 1). The ACZ treatment group continued to show more frequent PPW at 3 months. Some eyes had resolution of the baseline folds while other eyes developed new folds (Table 2, Figure 1). Among eyes, there was no consistent pattern of changes for all 3 types of folds, with eyes both resolving and developing 1 or more types of folds (Figures 1–3). In fact, there were eyes in both treatment groups where 1 type of fold resolved and another developed. ACZ-treated, but not placebo-treated, eyes showed significant reduction of RF at 3 and 6 months compared with baseline. At 6 months ACZ-treated eyes had fewer PPW (P = .022), whereas placebo-treated eyes had more PPW (P = .016). Except at 6 months, CF changes were not significantly changed over time or with therapy. Folds of all types affecting the macula were significantly fewer at 3 months (7 [16%] vs 17 [40%]) and 6 months (6 [14%] vs 16 [37%]) than at baseline in the ACZ-treated eyes only. The creases, corresponding to high-water marks, persisted in all eyes at 3 and 6 months (Figure 2) and 2 of the placebo group eyes had a new crease at 6 months.

Because in different eye some folds resolved and others developed (Tables 1 and 2), at 3 months (data not shown) there appeared to be no significant difference in the changes of the ONH shape, RNFL thickness, ONH volume, or Frisén grade when grouped (using ANOVA) by whether the PPW, RF, or CF were resolved, unchanged, or newly seen.

In contrast, at 6 months (Table 3), there was significant change (reduction) in the RNFL thickness, ONH volume and Frisén grade in eyes that had resolved RF, but not in eyes that had resolved PPW or CF. For change (both resolution and new folds) of RF, the change in RNFL thickness (r = −0.37, P = .001), ONH volume (r = −0.38, P = .001), and Frisén grade (r = −0.34, P = .002) correlated. For both improvement and worsening of folds affecting the macula, the change in RNFL thickness (r = −0.25, P = .025), ONH volume (r = −0.37, P = .001), and Frisén grade (r = −0.43, P = .001) correlated. Reduction in abnormal ONH shape was not significantly greater in eyes with improved PPW, RF, or CF. The CSFp was significantly reduced (29 ± 99 cm H2O vs 82 ± 102 cm H2O, P = .007) only in eyes that had resolved CF.

At 6 months, all 3 types of folds were still seen but RF were significantly less frequent (Table 3). Folds were seen even in eyes with Frisén grade 0 or 1 papilledema, although they were less frequent. Of the 2 eyes with grade 0, 1 eye had folds, which were PPW. Of the 25 eyes with grade 1, 9 had PPW, 6 with RF and 3 with CF (Figure 3). Of the 60 eyes with grade 2 or worse, 31 had PPW, 22 had RF, and 2 had CF.

The baseline ganglion cell layer + inner plexiform layer (GCL+IPL) thickness (similar with macula folds, 86.1 μm, and without macula folds, 84.6 μm, P = .32) and the 6-month GCL+IPL thickness were not different in eyes...
TABLE 2. Change in Folds at 3 and 6 Months by Type of Fold and Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Peripapillary Wrinkles</th>
<th>Retinal Folds</th>
<th>Choroidal Folds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resolved</td>
<td>No Change</td>
<td>New Folds</td>
</tr>
<tr>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>ACZ (n = 44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>5 11%</td>
<td>29 66%</td>
<td>10 23%</td>
</tr>
<tr>
<td>6 months</td>
<td>7 16%</td>
<td>34 77%</td>
<td>3 7%</td>
</tr>
<tr>
<td>Placebo (n = 43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>3 7%</td>
<td>34 79%</td>
<td>6 14%</td>
</tr>
<tr>
<td>6 months</td>
<td>3 7%</td>
<td>32 74%</td>
<td>8 19%</td>
</tr>
</tbody>
</table>

ACZ = acetazolamide.

FIGURE 1. At baseline, the images of the right eye over time show grade 3 papilledema (Top row, left); en face image at the level of the internal limiting membrane (ILM) shows horizontal radial retinal folds seen around the disc that are horizontal and most prominent at the temporal border of the left optic disc (Second row, left); 5-line horizontal raster image through the middle of the optic disc shows retinal pigment epithelium/Bruch membrane (RPE/BM) layer is inward deviation, identified by the arrow (retinal nerve fiber layer [RNFL] 358 μm and optic nerve head [ONH] volume 17.05 mm³), but does not show folds (Bottom row, left). At 3 months with acetazolamide (ACZ) treatment, the papilledema is improved (Top row, middle left); the retinal folds are gone but peripapillary wrinkles (PPW; arrows) have developed (Middle left column). At 6 months, the papilledema is grade 1 and has further resolved (Middle right column); the PPW (arrows) are still present (Middle right column); the RPE/BM layer is in the normal outward position (RNFL 111 μm and ONH volume 11.25 mm³). At 12 months, the images are normal (Right column).
with (84 μm) and without (82 μm, P = .2) macula folds. In addition, the mean GCL+IPL thickness was similar in eyes where macula folds improved (81.9 μm), were unchanged (82.5 μm), or worsened (81.1 μm).

At 6 months, eyes without folds affecting the macula had more high-contrast acuity letters seen than did eyes with folds affecting the macula (58.9 ± 5.0 vs 56.2 ± 6.1, P = .04), a trend of better MD (−2.17 ± 1.52 dB vs −2.70 ± 1.66 dB, P = .18), and a similar number of low-contrast visual acuity letters seen (27.9 ± 9.2, vs 27.2 ± 9.2 in eyes with folds, P = .89). The presence of any type of fold outside of the macula region did not correlate with any measure of vision performance at 6 months.

**DISCUSSION**

**FIGURE 2.** At baseline (Left column), the images of the right eye over time show grade 2 papilledema; radial retinal folds (arrows) extending temporally from the optic disc to the macula by en face imaging at the level of the ILM that is not seen on the horizontally oriented 5-line raster image (retinal pigment epithelium/Bruch membrane [RPE/BM] layer inwardly deviated) but is seen by vertically oriented reconstructed images through the macula region (Left column, bottom) (retinal nerve fiber layer [RNFL] 336 μm and optic nerve head [ONH] volume 17.0 mm³). At 3 months (Middle column) with acetazolamide (ACZ) treatment, the papilledema has improved; retinal folds are still present but less prominent (Middle column, second row) and are not seen on the low-resolution vertical reconstructed image (Middle column, third row); the RPE/BM layer has moved outward (Second column, bottom row). At 6 months, all images are normal (Right column) (RNFL 92 μm and ONH volume 11.9 mm³).

THIS STUDY SHOWED THAT THE VARIOUS TYPES OF FOLDS (ie, PPW, RF, CF, and creases) in eyes with papilledema can change over 6 months. RF were the only type that consistently decreased in frequency as papilledema...
resolved (based on a reduction of the mean RNFL, ONH volume, and Frisén grade). Given the known treatment effect, this was particularly evident in the ACZ group. There was no significant difference in the frequency of PPW or CF between treatment groups at 6 months. However, there was an unanticipated delay in the development of PPW in both treated and placebo groups at 3 and 6 months, as the papilledema began to recede. CF, once formed, tended to persist irrespective of the degree of papilledema. At 6 months, persistence or resolution of PPW or RF did not appear to be related to the CSF opening pressure or its change over time. CF, however, showed a very modest correlation with the CSF opening pressure and its change over the 6-month period.

Intracranial hypertension-caused increase in the retrolaminar tissue pressure, axoplasmic stasis, expansion of the volume of the ONH, and pressure at the scleral flange, resulting in folds in the retina and choroid that extend well beyond the ONH. Our baseline study correlated the types and patterns of folds with each of these mechanical forces. At baseline, PPW were associated with higher grades of papilledema (ie, greater mean Frisén grade, ONH volume, and RNFL thickness). CF were associated with anterior deformation of the peripapillary RPE/BM layer. RF were associated with both higher degree of papilledema and anterior deformation of the peripapillary RPE/BM layer. CF were the only type associated with higher levels of CSF opening pressure.

The association between the type of folds and structural parameters observed at baseline did not apply in all eyes during the 6-month follow-up. The findings in this follow-up study show that the relationships between folds and structural parameters are more complex and presumably reflect fundamental differences in the underlying mechanisms that cause each type of fold. This may in part be owing to the adaptive response of specific ocular

FIGURE 3. At baseline (Left column) the photo shows grade 2 papilledema (retinal nerve fiber layer [RNFL] 110 μm, optic nerve head [ONH] volume 12.4 mm³) (Top left) of the left eye; en face images at the level of the retinal pigment epithelium (RPE) shows horizontal choroidal folds (CF) around the optic disc and through the macula (Middle row, 2 left images); the 5-line raster images through the papillomacular region of the retina show the CF and overlying retinal folds (Bottom left). At 6 months (Right column) with placebo treatment, grade 2 papilledema remains (Top right); and the CF appear unchanged (Middle row, 2 right images, and Bottom right) (RNFL 120 μm, ONH volume 12.9 mm³).

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### TABLE 3. Change From Presentation for Optic Nerve Head Shape, Retinal Nerve Fiber Layer Thickness, Optic Nerve Head Volume, and Frisén Grade Grouped by the Change in Peripapillary Wrinkles, Retinal Folds, and Choroidal Folds at 6 Months, With Bonferroni Correction

<table>
<thead>
<tr>
<th>Papilledema Feature Change</th>
<th>Fold Change</th>
<th>PPW, N</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>95% CI</th>
<th>RF, N</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>95% CI</th>
<th>CF, N</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>95% CI</th>
<th>P Value Between-Groups</th>
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<tbody>
<tr>
<td>ONH shape</td>
<td>Resolved</td>
<td>19</td>
<td>-.13</td>
<td>1.58</td>
<td>-.94, 1.58</td>
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<td>20</td>
<td>-.66</td>
<td>1.70</td>
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<td>.34</td>
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<td>-1.02</td>
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<td>1.96</td>
<td>-.54, 1.96</td>
<td>57</td>
<td>.13</td>
<td>1.91</td>
<td>-.40, .67</td>
<td>77</td>
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<tr>
<td>New folds</td>
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<td>-.95, 1.89</td>
<td>8</td>
<td>.51</td>
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<td>RNFL thickness</td>
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<td>218</td>
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<td>1.1</td>
<td>0.7, 1.1</td>
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<td>19</td>
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<td>1.0</td>
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<td>.6</td>
<td>0.96</td>
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<tr>
<td>New folds</td>
<td>19</td>
<td>0.5</td>
<td>0.8</td>
<td>0.2, 0.8</td>
<td>19</td>
<td>0</td>
<td>0.5</td>
<td>-0.4, 0.4</td>
<td>2</td>
<td>0</td>
<td>1.4</td>
<td>-3.5, 0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CF = choroidal folds; CI = confidence interval (95th percentile); ONH = optic nerve head; PPW = peripapillary wrinkles; RF = retinal folds; RNFL = retinal nerve fiber layer; Std. Dev. = standard deviation.

For ONH shape (eigenvalue of the second principal component) change, minus is used for posterior direction movement away from the vitreous for the retinal pigment epithelium/Bruch membrane neural canal border. For RNFL thickness (μm), ONH volume (mm³), and Frisén grade change, positive is for less thickness or swelling. Note that for both resolved and worse change of the PPW, the RNFL thickness, ONH volume, and Frisén are less swollen or decreased. N is the number of study eyes with the specific type of fold.
tissues to stress and strain induced by changes in the elevated CSFp, ONH edema, and local tissue dynamics and environment.

For RF, it is possible that the forces imposed on the inner retinal layers are milder and well within the elastic limits of the ocular tissue involved. In support of this hypothesis, 12 of the 21 eyes that had resolution of RF at 6 months were Frisén grade 2 or worse and 11 eyes still had RNFL thickness greater than 120 μm (data not shown), which is well beyond the 95th percentile for swelling. Resolution of RF is correlated with reduction in papilledema; thus seeing fewer RF suggests improvement even in eyes with persistent papilledema.

PPW, the OCT demonstration of surface “Paton lines,” appear to be a consequence of combined internal compressive forces of the ONH and tensile hoop stress at the disc margin as the optic nerve head radially expands into the vitreous and surrounding retina.1 The correlation between PPW and ONH volume, observed at presentation, decreased over time owing to the delayed appearance of wrinkles as papilledema resolved.22,23 Specifically, in some eyes the PPW were absent in the acute severe stages of papilledema and only emerged as the disc edema improved. This may represent a “delayed elastic response.”24 Thus, persistence of PPW alone cannot be used to determine whether the papilledema is worsening or improving.

Because many eyes with CF did not change over time and persisted irrespective of the magnitude of changes in papilledema, observing CF is not useful for monitoring papilledema improvement. This is consistent with previous reports describing patients who present with choroidal folds in the absence of papilledema, thought to be attributable to past intracranial hypertension.25,26 The persistence of CF may reflect the adaptive remodeling of the outer retinal and RPE layers and other ocular tissues in response to prior or chronic elevated pressure on the scleral flange. The process would be akin to remodeling of the lamina cribrosa owing to chronic elevation of intraocular pressure (ie, cupping in glaucoma).27 Creases appear to be attributable to apposition of the structures in the outer retinal layers (ellipsoid to outer nuclear) as a result of having folds. Creases persist at 6 months (of note, in 1 eye at 1 year the crease and high-water mark resolved; Figure 4), even as the papilledema and retinal folds abate. Cell adhesion or chronic changes in the tissue may interfere with unfolding of the creases.

Visual performance at 6 months, based on the MD of threshold perimetry and high- and low-contrast acuity, was not measurably affected by the presence of PPW or retinal or choroidal folds, except when the folds involved the macula. In our cohort of IIH patients with mild visual field loss, few of whom developed major vision loss, only high-contrast visual acuity was reduced in the eyes with persistent macula folds.

In summary, retinal and choroidal wrinkles and folds are manifestations of stress and strain imposed on the globe by intracranial hypertension. In the early stages,
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REFERENCES


