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

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Abstract

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

Design/Study Subjects—Substudy of a randomized clinical trial.

Methods—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, 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—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.

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At 6 months, ACZ-treated, but not PLB-treated, eyes had fewer folds of all types ($p < 0.01$), 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. Trial registration: clinicaltrials.gov identifier: NCT01003639

Keywords

retinal folds; peripapillary wrinkles; choroidal folds; papilledema; idiopathic intracranial hypertension

Introduction

The Optical Coherence Tomography (OCT) Sub-Study of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) described several types of retinal and choroidal folds in patients with papilledema due to IIH with mild vision loss prior to treatment at presentation.¹ The most common were (i.) concentric or spiral peripapillary wrinkles (PPW) located in the retinal nerve fiber layer (RNFL) (ii.) horizontal or radial retinal folds (RF) in the inner and middle layers that spared the choroid and (iii.) 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 types 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 stereo photographs 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.³

The goal of this report is to describe the changes in the retinal and choroidal folds over 6 months due to IIH with and without treatment. We also determined if the presence of folds correlated with changes in of the degree of papilledema, the optic nerve head (ONH) neural canal border retinal pigment epithelium (RPE)/Bruch's membrane (BM) displacement and CSF pressure. Given the findings at baseline, we hypothesized: 1. Fewer PPW, RF and CF would be seen with reduction in the Frisén grade, mean retinal nerve fiber layer (RNFL) thickness and ONH volume over time; 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 sub-study of the IIHTT who had adequate OCT scans to evaluate the various folds at all visits during six month treatment interval. The IIHTT study design, patient selection, clinical profiles and outcome have been

published elsewhere.²⁻⁴ Briefly, newly diagnosed, untreated patients with IHH who had a mean deviation (MD) of -2.00 to -7.00 dB (Humphrey Field Analyzer II, SITA standard 24-2 test pattern, Carl Zeiss Meditec, Inc, Dublin, CA) 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 photos, best corrected high and low contrast visual acuity, threshold 24-2 perimetry, cerebrospinal fluid pressure, refractive error and SD-OCT imaging (using Cirrus 4000 SD-OCT, 6.01 software, Carl Zeiss Meditec, Inc, Dublin, CA) 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 IRB, the institution of NORDIC Headquarters. The study complied with the Declaration of Helsinki. We selected month six for analysis for correlating change because: 1. This was the IIHTT study outcome time point, with a strict protocol controlled therapeutic intervention; 2. There was a CSF pressure measurement obtained at six months for correlation. We utilized photos and OCT images up to the 12 months to demonstrate some key points.

All study sites followed a specific protocol for photos and SD-OCT image collection. Stereo pair fundus photographs centered on the optic disc and macula were obtained from each site using a minimum of a three megapixel fundus camera capable of imaging a 30°-35° 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 9mm horizontal high-definition (HD) 5-line Raster Scan at 0.5 mm intervals across the central surface of the optic disc, 2) two optic nerve head centered volume scans, and 3) two 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 SD-OCT to view the retina at the internal limiting membrane, middle layers and outer retina/retinal pigment epithelium levels to for each type of fold. Study eye images were evaluated by evaluators masked to the baseline results and treatment group assignment.

We utilized the features for each type of fold previously defined and used in the analysis of the baseline results.¹ Briefly, peripapillary wrinkles (PPW) are closely spaced circumferential undulations on the disc surface or within a half a disc diameter in the RNFL. Retinal folds (RF) are periodic surface or intraretinal radial or horizontal undulations greater than half a disc diameter from the disc. We restricted the diagnosis of choroidal folds (CF) to those eyes with undulations in the retinal pigment epithelium / Bruch's membrane (RPE/BM) 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 six 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 retinal pigment epithelial/Bruch’s membrane layer towards the vitreous (eigenvalue of the second principal component; negative values were for deformations towards the vitreous and positive values were 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 mean deviation. 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.^{2,6,10}

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 three or six month evaluations.

IBM SPSS statistical software version 23 (IBM, Inc.) was used for biostatistical evaluation of the data.¹¹ The McNemar test was used to test significance for follow up exam frequency of PPW, RF, and CF in each treatment group. The two-sided Fisher Exact test was used to test significance between treatment groups for PPW, RF, and CF. Analysis of variance was used to compare the **change** the in RNFL, ONH volume, ONH shape deformation, Frisén grade, CSF pressure (performed only at baseline and six months) and the **change** 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. Non-parametric correlations were made between the present or absent of each type of fold with RNFL thickness, ONH volume, ONH shape deformation, Frisén grade, high and low contrast visual acuity, and mean deviation. Given the low prevalence of creases, we only report the observed 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, 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 ($p = 0.001$). Creases affected three eyes in the ACZ group and six eyes in the placebo group at baseline. The folds affected the macula 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 ($279 \pm 165 \mu\text{m}$) and ONH volume ($16.5 \pm 3.8 \text{ mm}^3$) at baseline were reduced for all study eyes at three months ($169 \pm 122 \mu\text{m}$ and $13.7 \pm 3.1 \text{ mm}^3$) and further decreased at six months ($139 \pm 85 \mu\text{m}$ and $12.7 \pm 2.3 \text{ mm}^3$). The baseline anterior displacement (towards the vitreous)

ONH shape (-0.29 ± 1.07) normalized in the posterior direction (away from the vitreous)¹¹ at three months (0.043 ± 0.91) and six months (0.27 ± 1.19). The ACZ treatment group was significantly improved for all three OCT measures compared with the placebo group.¹¹ Also, as previously reported, the ACZ treated group had greater reduction in CSF pressure at six months, but 15 subjects in the ACZ group as well as 25 placebo treated subjects had six month opening pressure elevation above 25 cm H₂O at six months, which we considered abnormal.

The frequency of all three types of folds changed at three and six months (Table 1a). The ACZ treatment group continued to show more frequent PPW at three months. Some eyes had resolution of the baseline folds while other eyes developed new folds (Table 1b, Figure 1). Among eyes, there was no consistent pattern of changes for all three types of folds with eyes both resolving and developing one or more types of folds (Figures 1–3). In fact, there were eyes in both treatment groups where one type of fold resolved and another developed. ACZ-treated, but not placebo-treated, eyes showed significant reduction of RF at three and six months compared with baseline. At six months ACZ-treated eyes had fewer PPW ($p=0.022$) while placebo treated eyes had more PPW ($p = 0.016$). Except at six months, CF changes were not significantly changed over time or with therapy. Folds of all types affecting the macula were significantly fewer at three months (7 [16%] vs 17 [40%]) and six 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 three and six months (Figure 2) and two of the placebo group eyes had a new crease at six months.

Because in different eye some folds resolved and others developed (Table 1), at three 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 six months (Table 2), 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 ($r = -0.37$, $p = 0.001$), ONH volume ($r = -0.38$, $p = 0.001$), and Frisén grade ($r = -0.34$, $p = 0.002$) correlated. For both improvement and worsening of folds affecting the macula, the change in RNFL thickness ($r = -0.25$, $p = 0.025$), ONH volume ($r = -0.37$, $p = 0.001$), and Frisén grade ($r = -0.43$, $p = 0.001$) correlated. Reduction in abnormal ONH shape was not significantly greater in eyes with improved PPW, RF, or CF. The CSF pressure was significantly reduced (29 ± 99 cm H₂O vs 82 ± 102 cm H₂O, $p = 0.007$) only in eyes that had resolved CF.

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

The baseline GCL+IPL thickness (similar with macula folds, $86.1 \mu\text{m}$, and without macula folds, $84.6 \mu\text{m}$, $p = 0.32$) and the six month GCL+IPL thickness were not different in eyes with ($84 \mu\text{m}$) and without ($82 \mu\text{m}$, $p = 0.2$) macula folds. In addition, the mean GCL+IPL thickness was similar in eyes where macula folds improved ($81.9 \mu\text{m}$), were unchanged ($82.5 \mu\text{m}$), or worsened ($81.1 \mu\text{m}$).

At six months, eyes without folds affecting the macula had more high contrast acuity letters seen than for eyes with folds affecting the macula, (58.9 ± 5.0 vs 56.2 ± 6.1 , $p = 0.04$), a trend of better mean deviation ($-2.17 \pm 1.52 \text{ dB}$ vs $-2.70 \pm 1.66 \text{ dB}$, $p = 0.18$), and similar number of low contrast visual acuity letters seen (27.9 ± 9.2 vs 27.2 ± 9.2 than for eyes with folds, $p = 0.89$). The presence of any type of fold outside of the macula region did not correlate with any measure of vision performance at six months.

Discussion

This study showed that the various types of folds (i.e. PPW, RF, CF and creases), in eyes with papilledema can change over six 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,^{4,12} this was particularly evident in the ACZ group. There was no significant difference in the frequency of PPW or CF between treatment groups at six months. However, there was an unanticipated delay in the development of PPW in both treated and placebo groups at three and six months, as the papilledema began to recede. CF, once formed, tended to persist irrespective of the degree of papilledema. At six 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 six month period.

Intracranial hypertension-caused increase in the retrolaminar tissue pressure, axoplasmic stasis, expansion of the volume of the ONH, pressure at the scleral flange,^{10,12} result in folds in the retina and choroid that extend well beyond the ONH.^{12,17–22} 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 (i.e. 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 six 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 due to the adaptive response of specific ocular tissues to stress and strain induced by changes in the elevated CSF pressure, 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 six 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’s lines,”^{8,9} 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 that radially expands into the vitreous and surrounding retina.¹ The correlation between PPW and ONH volume, observed at presentation, decreased over time due to the delayed appearance of wrinkles as papilledema resolved.^{23,24} 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”.²⁵ Thus, persistence of PPW alone cannot be used to determine whether the papilledema is worsening or improving.

Since many eyes with CF did not change over time and persisted irrespective of the magnitude or 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 due to past intracranial hypertension.^{26,27} 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 due to chronic elevation of intraocular pressure, i.e. cupping in glaucoma.²⁸

Creases appear to be due to apposition of the structures in the outer retinal layers (ellipsoid to outer nuclear) as a result of having folds. Creases persist at six months (Of note in one eye at one 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 six months, based on the mean deviation of threshold perimetry, high and low contrast acuity, was not measurably affected by the presence of PPW, 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, the pattern and location of folds are the results of the effects of papilledema severity, peripapillary anterior deformation of the scleral flange, stiffening in the optic nerve sheath, and distortion and displacement of the lamina cribrosa and soft tissues of the optic nerve head. These effects are also modulated by individual differences in structural anatomy and material properties, which includes bending stiffness, of the optic nerve head and retinal layers.^{29–35} While this basic scheme would seem to explain the behavior of RF as papilledema and intracranial

hypertension resolve, the delayed development of PPW and the persistence of CF irrespective of the degree of papilledema or intracranial pressure suggest an adaptive response over time.

There are some caveats in our conclusions. Our method for evaluating the folds and wrinkles is qualitative; more quantitative measurements might show changes over time or with therapy. Further, 34% of subjects in the ACZ group and 58% in the placebo group had continued elevated CSF pressure. Even though the intracranial pressure was frequently decreased, the continued effect of elevated pressure and forces could contribute to persistence of the folds even as the OCT and photographic measures of papilledema were reduced.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

At baseline the right eye shows grade 3 papilledema (top left); *en face* image at the level of the internal limiting membrane (ILM) shows horizontal radial retinal folds seen around on 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's 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 mm^3] but does not show folds (bottom row left). At three months with acetazolamide (ACZ) treatment, the papilledema is improved (top row left); the retinal folds are gone but peripapillary wrinkles [PPW (arrows)] have developed (middle left column). At six 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 mm^3). At 12 months, the images are normal (right column).

Figure 2.

At baseline (left column), the right eye shows 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 horizontal oriented 5 line raster image (RPE/BM layer inwardly deviated) but is seen by vertically oriented reconstructed images through the macula region (left column bottom) (RNFL 336 μm and ONH volume 17.0 mm^3). At three months (middle column) with ACZ treatment, the papilledema has improved; retinal folds are still present less prominent (middle column second row) and 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 six months, all images are normal (right column) (RNFL 92 μm and ONH volume 11.9 mm^3).

Figure 3.

At baseline (left column) the left eye shows grade 2 papilledema (RNFL 110 μm , ONH volume 12.4 mm^3) (top left) of the left eye; *en face* images at the level of the RPE shows horizontal choroidal folds (CF) around the optic disc and through the macula (two left middle images); the 5 line raster images through the papillomacular region of the retina show the CF and overlying RF (bottom left). At six months (right column) with placebo treatment, grade 2 papilledema remains (top right); and the CF appear unchanged (right middle and bottom) (RNFL 120 μm , ONH volume 12.9 mm^3).

Figure 4.

At baseline (left column), the right eye shows grade 4 papilledema and a “high water mark” (white arrowhead) which corresponds to the crease (black arrowhead) in the 5 line raster image that shows the RPE/BM layer deviated inward (RNFL 453 μm and ONH volume 20.21 mm^3); the high water mark (white arrowhead) and corresponding crease (black arrowhead) persist at three months (middle left column) and at six months (middle right column) as the papilledema improved (grade 3) (RNFL 169 μm and ONH volume 14.47 mm^3) with ACZ treatment; by 12 months, the papilledema and crease are resolved and the RPE/BM layer position is restored in the outward direction (right column).

Table 1

a: Frequency by type of fold at 3 and 6 months in treated and placebo groups											
ACZ (n=44)						Placebo (n=43)					
Peripapillary Wrinkles											
Baseline		28	(63.6%)		12	(27.9%)					
3 months		28	(63.6%)*		15	(34.9%)					
6 months		24	(54.5%)**		17	(39.5%)					
Retinal folds											
Baseline		21	(47.7%)		23	(53.5%)					
3 months		12	(27.3%***)		22	(51.2%)					
6 months		9	(20.5%)+, ****		22	(51.2%)					
Choroidal folds											
Baseline		7	(15.9%)		3	(7%)					
3 months		3	(3.8%)		2	(4.7%)					
6 months		3	(3.8%)+, ++		2	(4.7%)					

b. Change in Folds at 3 and 6 months by type and treatment group												
Peripapillary Wrinkles				Retinal folds				Choroidal folds				
resolved		No change		New folds		resolved		No change		New folds		
ACZ (n=44)	n		n		n		n		n		n	
3 months	5	11%	29	66%	10	23%	10	23%	33	75%	1	2%
6 months	7	16%	34	77%	3	7%	11	25%	33	75%	0	0%
Placebo (n=43)												
3 months	3	7%	34	79%	6	14%	7	16%	30	70%	6	14%
6 months	3	7%	32	74%	8	19%	9	21%	26	60%	8	19%

n is the number of eyes in each group

Comparison between ACZ and Placebo groups:

* p=0.001;

** p=0.007;

*** p=0.019;

No other values significant difference between treatment groups or change over time

++p=0.032

+p=0.001;

Change from baseline for ACZ group:

***d=0.003

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Table 2

Change from presentation for optic nerve head (ONH) shape, retinal nerve fiber layer (RNFL) thickness, optic nerve head volume and Fris n grade grouped by the change in peripapillary wrinkles (PPW), retinal folds (RF), and choroidal folds (CF) at six months – with Bonferroni correction. For optic nerve head 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's membrane neural canal border. For retinal nerve fiber layer thickness (µm), optic nerve head volume (mm³), and Fris n grade change positive is for less thickness or swelling.

Papilledema feature change	Fold change	PPW N	Mean	Std. Dev.	95% CI	P value between groups comparison	RF N	Mean	Std. Dev.	95% CI	P value between groups Comparison	CF N	Mean	Std. Dev.	95% CI	P value between groups comparison
ONH Shape	Resolved	19	-0.13	1.58	-0.94, 1.58	1.0	20	-.66	1.70	-1.48, .16	.34	6	-1.02	1.1	-2.2, 0.2	0.38
	No change	46	0.09	1.96	-.54, 1.96		57	.13	1.91	-.40, .67		77	.044	1.9	-.04, 0.5	
	New folds	19	-.04	1.89	-.95, 1.89		8	.51	1.71	-1.07, 2.09		2	.497	.26	-1.8, 2.8	
RNFL Thickness	Resolved	19	222	206	123, 206	.16	20	218	196	126, 310	.021	6	188	201	2, 374	0.58
	No change	43	83	137	38, 137		54	105	143	65, 146		74	120	160	81, 158	
	New folds	19	122	132	59, 132		8	20	57	-33, 80		2	141	145	-1161, 1443	
ONH volume	resolved	18	5.91	4.33	3.8, 4.3	.07	20	5.64	4.32	3.6, 7.7	.011	6	5.87	4	2.2, 9.6	0.81
	No change	43	2.34	3.21	1.3, 3.2		53	2.94	3.14	2, 3.8		73	3.18	3.6	2.3, 4.0	
	New folds	19	3.29	2.88	1.9, 2.9		8	.57	1.32	-6, 1.8		2	3.10	3.6	-29.7, 35.9	
Frisén Grade	resolved	17	1.3	1.1	0.7, 1.1	.07	19	1.2	1.1	0.6, 1.7	.020	6	1.6	1.3	0.4, 2.7	.061
	No change	45	0.5	1.0	0.2, 1.0		54	0.6	1.0	0.4, 0.9		74	.6	0.96	0.4, 0.9	
	New folds	19	0.5	0.8	0.2, 0.8		19	0	0.5	-0.4, 0.4		2	0	1.4	-3.5, 0.4	

Note that for both resolved and worse change of the peripapillary wrinkles, the retinal nerve fiber layer thickness, optic nerve head volume and Fris n are less swollen or decreased. N is the number of study eyes with the specific type of fold. Std. dev. is the standard deviation. The confidence interval (CI) is the 95th percentile.