Photographic Reading Center of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT): Methods and Baseline Results

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PURPOSE. To describe the methods used by the Photographic Reading Center (PRC) of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) and to report baseline assessments of papilledema severity in participants.

METHODS. Stereoscopic digital images centered on the optic disc and the macula were collected using certified personnel and photographic equipment. Certification of the camera system included standardization and calibration using a model eye. Lay readers assessed disc photos of all eyes using the Frisén grade and performed quantitative measurements of papilledema. Frisén grades by PRC were compared with site investigator clinical grades. Spearman rank correlations were used to quantify associations among disc features and selected clinical variables.

RESULTS. Frisén grades according to the PRC and site investigator's grades, matched exactly in 48% of the study eyes and 42% of the fellow eyes and within one grade in 94% of the study eyes and 92% of the fellow eyes. Frisén grade was strongly correlated ($r > 0.65$, $P < 0.0001$) with quantitative measures of disc area. Cerebrospinal fluid pressure was weakly associated with Frisén grade and disc area determinations ($r \leq 0.31$). Neither Frisén grade nor any fundus feature was associated with perimetric mean deviation.

CONCLUSIONS. In a prospective clinical trial, lay readers agreed reasonably well with physicians in assessing Frisén grade. Standardization of camera systems enhanced consistency of photographic quality across study sites. Images were affected more by sensors with poor dynamic range than by poor resolution. Frisén grade is highly correlated with quantitative assessment of disc area. (ClinicalTrials.gov number, NCT01003639.)

Keywords: clinical trials, papilledema, idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is diagnosed based on symptoms of headache, transient obscurations of vision, and pulsatile tinnitus as well as signs of papilledema and high cerebrospinal fluid (CSF) pressure with normal spinal fluid composition and normal brain imaging.¹ Untreated, the disease can lead to permanent visual loss in up to 25% to 50% of patients.² The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), performed under the auspices of the Neuro-Ophthalmology Research Investigators Consortium (NORDIC), was the first prospective randomized, double-masked clinical trial that evaluated the efficacy of acetazolamide plus diet compared with diet alone in the treatment of IIH. Inclusion and exclusion criteria have been described in a prior publication. The study eye was the eye with the worst perimetric mean deviation (PMD) at baseline.³ To provide consistent grading and to document the clinical changes in papilledema, standardized fundus photography was evaluated by a Photographic Reading

Center (PRC). Frisén grading at month 6 was a secondary outcome variable in the trial. The purpose of this article is to describe the methods used by the PRC, and to report on the fundus findings at baseline for participants enrolled in the IIHTT.

METHODS

Standardization of Photographic Images

Multicenter clinical trials requiring ocular fundus photography have been performed historically using photographic film. However, in recent years film has been almost entirely replaced by electronic imaging using high-resolution complementary metal-oxide semiconductor or charge-coupled device cameras. Whereas film can be easily standardized in terms of resolution and color temperature, electronic image capture is highly

FIGURE 1. The model eye was developed to provide uniformity in photographic images across multiple sites participating in the IIHTT study. (a) The model eye mounted to a fundus camera. (b) The curved rear plane designed to emulate the retinal curvature. (c) The calibration target that is adhered to the rear curved surface with both color and linear calibration targets.

variable and often user-adjustable.^{4,5} Hubbard et al.⁴ previously demonstrated that digital enhancement of color by changing the red, green, and blue channel histograms improved readability of the digital images to be comparable to that of film. Danis et al.⁶ of the Age-Related Eye Disease Study 2 Study Group (AREDS2) compared seven approved digital cameras to film for AMD features and found no differences between film and digital imaging, with agreement for Age-Related Eye Disease Study (AREDS) and AREDS2 contemporaneous sample of 93.6% and 95.6%, respectively.

To standardize fundus images from the 38 enrollment sites, minimum requirements were set for the equipment, a model eye was developed as an independent standard for color and resolution, and a detailed operational protocol was established.

Based on the area of interest and the details to be evaluated, sites were required to have a retinal fundus camera with a digital imaging sensor with a minimum resolution of three megapixels capable of imaging at either a 30° or 35° field of view. To maintain image quality, full-resolution uncompressed Tagged Image File Format images were acquired and submitted to the PRC through electronic upload.

A model eye shown in Figure 1a was developed for the project to allow the PRC to incorporate magnification scale factors and color correction specific to each camera and sensor configuration. The calibration model eye is substantially representative of the colors of the retina, optic disc, and retinal vessels. Fundus cameras are designed to image a curved

plane sharply focused on the flat plane of the imaging sensor. The model eye incorporated a curved rear surface that emulated the curved surface of the retina (Fig. 1b). The test target in the model eye included a linear bar for magnification and scale factor calculations as well as a series of color swatches that represented a range of fundi colors typically seen (Fig. 1c).

Sites were certified for participation in the study in a two-step process: system certification and photographer certification. At the onset of the study and whenever a new camera was used, sites photographed the model eye and submitted the images to the PRC for review and image calibration. Once the camera was approved, the site returned the model eye to the PRC.

Two nonstudy subjects were photographed following the study guidelines for magnification, focus, exposure, and retinal position within the frame and were submitted to the PRC for certification. Sites were instructed to adjust exposure to maintain detail of the optic nerve. This sometimes proved challenging with older sensors with limited dynamic range. Dynamic range is the ability to maintain separation of tones from lighter areas to darker areas. Poor dynamic range led to loss of detail and uncertainty in grading the highly reflective disc and the darker retina for both Frisén grading and quantitative assessment. The PRC evaluated the images for proper field of view (magnification), resolution, focus/clarity, stereographic effect, and field positioning. To submit images,

FIGURE 2. Two different planes of focus were used to image the papilledema. (a) Focused on the dome of the disc with the area of “white” elevation outlined in yellow. (b) Focused on the base of the disc closer to the plane of the retina with the area of “total” elevation outlined in green. Each image is used to identify key features based on the Frisén scale. Note that vascular attenuation on the disc substance varies substantially depending on the plane of focus.

FIGURE 3. A feature grid overlay is used as an aid in quantitative measurement of papilledema features. The diameter of the inner circle is 1800 μm , the middle circle is 3600 μm , and the outer circle is 5400 μm . Blood vessel measurements were taken in each quadrant in which the major artery and vein cross the outer circle.

sites used a software client installed on a local computer, providing secure data transfer of the images from the site to the PRC servers.

The pupils of study subjects were dilated and imaging occurred when the pupil was 6 mm or larger. A complete set of images included four stereo pairs of each eye. Two stereo pairs of the optic disc were taken; one stereo pair focused on the apex of the disc and a second pair focused on the base of the disc (Figs. 2a, 2b). One stereo pair of the macula was taken. One stereo pair imaged the fundus red reflex to document any media opacities or other issues that could interfere with high-quality images.

Using the upload client installed on a local computer, the site entered the following data: subject identification number (subject ID), photographer identification code (photographer ID), date of service, visit/month from a pull-down menu, camera identification number (camera ID) from a pull-down menu, subject's date of birth, and best corrected visual acuity (BCVA) refraction for the date of service. The images, along with the subject information, were securely transmitted to the PRC. On successful transmission of the data, the system automatically transmitted an e-mail receipt verifying the submission.

An approximation of the axial length using the Bengtsson and Krakau equation and the subject's BCVA refraction for each visit was used to create a scale factor that was applied to each measurement.⁷

The PRC system had image zoom capabilities, brightness, and contrast adjustment, and text annotation features. The software contained a ruler tool that measured in microns and a circle/oval tool for outlining the border of the optic nerve. This allowed the area of the optic cup to be calculated in square millimeters. The arterial-venous ratio (A:V ratio) was calculated as follows: the diameter of each major artery and vein in each quadrant was measured, and all of the artery and vein diameters were summed over quadrants. The A:V ratio for the eye was calculated as the ratio of the summed diameters for the artery and the summed diameters for the vein. A feature grid consisted of a series of three concentric circles with diameters of 1800, 3600, and 5400 μm (approximately one,

two, or three disc diameters) as well as radial lines that segmented the circles into clock hours (Fig. 3). The feature grid was used when performing linear blood vessel measurements at predetermined distances from the optic nerve. It also functioned as a tool that allowed for quantification, by clock-hour or quadrant, of the number of hemorrhages or other focal retinal pathologies.

Measures of Disc Edema

Two types of photographic measures were included in the assessment. The principal measure was the Frisén grade, previously validated as a means of assessing papilledema in IIH patients.^{8–10} This grading system provided for semi-quantitative categorization of papilledema from absent to severe on a scale of 0 to 5, with 0 being no papilledema and 5 being severe papilledema. The characteristics for grading are shown in Table 1.⁸ Another assessment of papilledema was a quantitative determination of multiple direct and calculated morphometric measures associated with photographic features of disc swelling. A number of prior photographic studies have attempted to look at optic disc edema and there are additional reports involving optical coherence tomography (OCT) and optic disc edema.^{8,11–13}

The Frisén grading system was standardized by creating an external photographic dataset consisting of 66 representative but de-identified fundus images centered on the optic disc.⁹ Three neuro-ophthalmology experts, Steven Feldon (SF), Michael Wall, and James Corbett, independently graded each of the images. The initial agreement of the expert panel members for both eyes occurred in 26 images (39%). In an adjudication meeting among the three experts, agreement was achieved in 33 additional images, resulting in agreement overall in 59 images (89%), whereas 7 (11%) were determined to be unclassifiable (Fig. 4). Based on the adjudication meeting, the grading criteria were refined and a provision was made to identify the presence or absence of disc pallor. From the independent, graded images, representative examples were incorporated into a “training set” that clearly illustrated the defining characteristics of each stage of papilledema. A lay

TABLE 1. Modified Frisén Scale of Papilledema

STAGE 0: Normal optic disc or not a normal disc but with no C-shaped halo
A. Prominence of the retinal nerve fiber layer at the nasal, superior, and inferior poles in inverse proportion to disc diameter
B. Radial nerve fiber layer striations, without tortuosity
STAGE I: Minimal degree of edema
A. C-shaped halo that is subtle and grayish with a temporal gap; obscures underlying retinal details*
B. Disruption of normal radial nerve fiber layer (NFL) arrangement striations
C. Temporal disc margin normal
STAGE II: Low degree of edema
A. Circumferential halo*
B. Elevation: nasal border
C. No major vessel obscuration
STAGE III: Moderate degree of edema
A. Obscuration of 1 or more segments of major blood vessels leaving disc*
B. Circumferential halo
C. Elevation: all borders
D. Halo: irregular outer fringe with finger-like extensions
STAGE IV: Marked degree of edema
A. Total obscuration of a segment of a major blood vessel on the disc*
B. Elevation: whole nerve head, including the cup
C. Border obscuration: complete
D. Halo: complete
STAGE V: Severe degree of edema
A. Partial obscuration of all vessels on disc and total obscuration of at least 1 vessel on disc*

Adapted from Scott CJ, Kardon RH, Lee AG, Frisén L, Wall M. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography versus clinical expert assessment using a clinical staging scale. *Arch Ophthalmol*. 2010;128:705-711.

* Defining characteristic of the stage.

panel of PRC readers was then trained using the training set until criteria for competency were reached. Lay readers were deemed “trained” when they were capable of correctly grading 75% of the training set images and were within one Frisén grade on 90% of the images. Although stereo pairs were created by the sites, only one image of any stereo pair was used for evaluation based on the methodology described by Frisén.⁹ Once the study was under way, the same five readers were used throughout the study. Any given image was read by two of the five trained lay readers. Readers determined the Frisén grade without referencing any prior or subsequent images and

without knowledge of vision status or treatment assignment. If two independent readers failed to agree on the Frisén grade, then the images were sent to a neuro-ophthalmology expert (SF) for adjudication. The expert was masked to the grading from the readers. During the first 6 months of the study, there were monthly sessions held between all readers and the expert to review images that required adjudication.

For quantitative assessment of papilledema, disc-centered stereo-paired images were selected for each subject’s right and left eyes. Stereo viewing was permitted to optimally assess each feature. Two readers independently assessed each image

FIGURE 4. This diagram outlines the process for developing the set of disc images used to train the lay readers on the Frisén grading system.

for all measurements. If there was more than a 10% discrepancy between any measurements, the two readers conferred to resolve differences. Very few discrepancies could not be resolved, and those were further adjudicated by the expert neuro-ophthalmologist (SF).

Two optic disc areas were identified for purposes of measurement. Most discs with papilledema demonstrated a highly reflective central component, which we termed as

“white” elevation, surrounded by a less-reflective peripheral component that still appeared to be elevated, termed “dark” elevation. The termination of “dark” elevation corresponded to the disappearance of swelling into the plane of the retina, accentuated by a distinctive change in direction of the retinal vessels. The “white” and “dark” areas together constituted the “total” elevation of the disc. These regions are shown in Figures 2a and 2b. Retinal features, including macular edema, macular star, and retinal hemorrhages, associated with papilledema also were evaluated.

Statistical Analysis

Weighted kappa statistics were used to assess the agreement between the PRC and the site investigator with respect to Frisén grades. Spearman rank correlations were used to quantify associations among features assessed in both the study eye and the fellow eye and selected clinical variables. In particular, the following associations were examined: Frisén grade with CSF pressure, body mass index (BMI), area of “white” elevation, area of “total” elevation, and various blood vessel cross-sectional diameters; and areas of “white” and “total” elevation with CSF pressure, BMI, and PMD.

RESULTS

Quality Measures

The percentage of images requiring adjudication decreased over time from 58% to 28% (Fig. 5). For all subjects, the adjudication rate was 33%. Ten percent of all of the images were submitted for masked re-reading. The agreement between the initial read and the re-read was 73% for reader 1, 63% for reader 2, 62% for reader 3, 56% for reader 4, and 55% for reader 5. All of the readers graded at least 93% of the re-reads within 1 grade of the original read (Fig. 6).

Retinal Features

The retinal features associated with papilledema and the individual measurements obtained for disc and retinal vessel

FIGURE 5. Images of the disc were assessed by two lay readers using the Frisén grading system. Over time, the percentage of images requiring expert adjudication (SF) was reduced from 58% to 28%.

FIGURE 6. Intrareader reliability was assessed by re-reading a random sample of 10% of the images. A total of five lay readers were used in the study. Their performance varied from 93% to 97% for identification within one grade (either exact match or one grade difference) of the initial reading, but varied from 55% to 73% for identification of the exact same Frisén grade. More than one Frisén grade disparity occurred rarely.

features are shown in Tables 2 and 3. Although cup-to-disc area ratios were examined, only 2% were measureable (cup > 0 mm²). The resulting data were set too small to provide meaningful data analysis. Other features of papilledema, such as cotton wool spots, exudates, and retinal/choroidal folds were seen. Although not measured as part of this study, these findings are a subject of current investigations.

Frisén Grading

The distribution of Frisén grades at baseline for enrolled subjects has been previously published.¹⁴ The frequencies of Frisén grades were approximately the same for study and fellow eyes, and there were only small differences between the PRC and site investigator (SI) grades. The PRC matched exactly the SI Frisén grade on 48% of study eyes and 42% of fellow eyes. The PRC was one grade lower than the SI Frisén grade on 21% of study eyes and 19% of fellow eyes. The PRC was one Frisén grade higher on 26% of study eyes and 31% of fellow eyes. The PRC and SI agreed within one Frisén grade on 94% of study eyes and 92% of fellow eyes. Two or more Frisén grade

differences between the PRC and SI were noted for 6% of study eyes and 8% of fellow eyes.¹⁴ Weighted kappa statistics demonstrated moderate agreement between the PRC and SI: $\kappa = 0.51$ (95% confidence interval [CI] 0.43–0.60) for the study eye and $\kappa = 0.45$ (95% CI 0.37–0.54) for the fellow eye. Symmetry between eyes according to the PRC Frisén grade was identified in 58% of subjects and an additional 35% had eyes that differed by one grade. In 32% of subjects, the study eye was worse, and in 10% of subjects, the fellow eye was worse. The degree of symmetry between the two eyes of each subject is shown in Figure 7.

Quantitative Assessment

We found strong associations between Frisén grade and the areas of “white” and “total” elevation for both the study eye and the fellow eye (Table 4). There were weaker but statistically significant positive correlations between CSF pressure and Frisén grade and to a lesser extent, between CSF pressure and the areas of “white” and “total” elevation (Table 4). The PMD was associated with the area of “white”

TABLE 2. Measured Retinal Features

Item	Fellow Eye			Study Eye		
	Mean	SD	n	Mean	SD	n
Disc area of white elevation, mm ²	6.44	2.81	158	7.01	2.89	158
Disc area of total elevation, mm ²	11.79	4.52	134	12.64	4.63	142
Disc vertical axis of white elevation, μ m	3133.10	737.60	158	3265.56	713.08	158
Disc horizontal axis of white elevation, μ m	2486.46	557.44	158	2618.34	549.15	158
Disc vertical axis of total elevation, μ m	4219.14	853.30	134	4365.29	833.63	142
Disc horizontal axis of total elevation, μ m	3439.98	652.32	134	3590.44	674.50	142
Diameter superior nasal vein, μ m	97.69	24.58	144	100.00	26.44	142
Diameter superior nasal artery, μ m	63.06	15.79	133	61.05	13.52	128
Diameter superior temporal vein, μ m	134.36	26.66	150	132.98	26.41	144
Diameter superior temporal artery, μ m	83.30	19.10	141	80.41	16.64	143
Diameter inferior temporal vein, μ m	139.40	28.17	143	143.57	27.55	138
Diameter inferior temporal artery, μ m	82.09	17.78	132	82.44	17.09	121
Diameter inferior nasal vein, μ m	97.25	24.14	144	98.23	24.40	142
Diameter inferior nasal artery, μ m	62.35	16.60	133	61.55	14.46	128

TABLE 3. Assessed Macular Features

Item	Fellow Eye				Study Eye			
	Yes	No	Questionable	Cannot Grade	Yes	No	Questionable	Cannot Grade
Macula edema present	7	141	13	4	15	130	18	2
Macular star present	1	164	0	0	2	163	0	0
Foveal reflex present	92	51	18	4	79	61	23	2
Hemorrhages within 1 disc diameter of macula	0	163	0	2	2	162	0	1

elevation for the fellow eye only and not with the area of “total” elevation in either eye (Table 4). The inconsistent association of disc areas with PMD paralleled the lack of association between PMD and Frisén grade.¹⁴

Larger arteries relative to veins (A:V ratio) were associated with decreased areas of “white” and “total” elevation in the study eye only. There were modest negative associations between the A:V ratio and both the area of “white” elevation ($r = -0.34$, $P = 0.0006$) and the area of “total” elevation ($r = -0.25$, $P = 0.02$) in the study eye only (Figs. 8a, 8b), suggesting that larger veins relative to arteries are associated with more papilledema. The A:V ratio was weakly correlated with Frisén grade in both the study ($r = -0.24$, $P = 0.02$) and fellow ($r = -0.19$, $P = 0.05$) eyes (Table 4; Fig. 8c) and no strong associations were found between the A:V ratio and PMD (Table 4).

DISCUSSION

This article describes a systematic and validated approach to Frisén grading and quantitative assessment of disc photographs in the context of a prospective, multicenter clinical trial using trained lay readers. The methodology developed and used by the PRC to manage the magnification and color differences among the available fundus cameras successfully produced high-quality standardized reliable photographic images collected from 38 study sites for PRC assessments.

Frisén Grading

Frisén proposed a semi-quantitative measure to assess the amount of optic disc swelling.⁹ Early stages of papilledema were observed to be associated with a “grayish, faintly reticulated halo,” whereas more advanced stages were noted to be associated with anterior tissue expansion causing obscuration of retinal vasculature overlying the optic disc.⁹ In Frisén’s initial validation of the grading system, three observers with varying levels of experience were able to achieve exact agreement in 49% and agreement within one grade in 86% of optic disc photographs.⁹

Sinclair et al.¹⁰ recently revisited the utility of the Frisén scale for use in IIH due to concerns that several disc changes were not included as part of the grading system, including vascular changes, hemorrhages, hyperemia, and infarcts. Another concern was that the scale did not accommodate resolving papilledema, including optic atrophy. Six expert, but not systematically trained, observers agreed completely with the Frisén grading in only 3 of 188 photographs (1.6%). Using pairs of reviewers to allocate Frisén grades for acute IIH, there was agreement in 36.3% and one grade of disagreement in 46.4%, or 83% agreement within one grade. With the IIHTT methodology for grading, lay readers obtained results similar to those of Frisén and Sinclair et al.¹⁰ with an overall adjudication rate of 32.5%. We conclude that well-trained lay readers can be effectively used in the context of multicenter clinical studies to

FIGURE 7. The Frisén grade of the fellow eye was subtracted from that of the study eye to evaluate the symmetry between eyes at baseline (study eye-fellow eye). On the horizontal axis, the values at 0 represent study eye and fellow eye Frisén grades that were equal. Values to the left of 0 represent study eye Frisén grades that were lower than the fellow eye Frisén grades. Values to the right of 0 represent study eye Frisén grades that were higher than the fellow eye Frisén grades.

TABLE 4. Correlations of Measured Variables

Variable	n	Correlation	P
(a) Correlations with Frisén grade			
Area of white elevation, study eye	158	0.68	<0.0001
Area of white elevation, fellow eye	158	0.72	<0.0001
Area of total elevation, study eye	142	0.65	<0.0001
Area of total elevation, fellow eye	134	0.67	<0.0001
(b) Correlations with CSF pressure			
Area of white elevation, study eye	158	0.17	0.03
Area of white elevation, fellow eye	158	0.19	0.02
Area of total elevation, study eye	142	0.18	0.04
Area of total elevation, fellow eye	134	0.27	0.001
Frisén grade, study eye	165	0.28	0.0002
Frisén grade, fellow eye	165	0.31	<0.0001
(c) Correlations with PMD			
Area of white elevation, study eye	158	0.02	0.77
Area of white elevation, fellow eye	158	−0.2	0.01
Area of total elevation, study eye	142	−0.01	0.89
Area of total elevation, fellow eye	134	−0.1	0.27
(d) Correlations with A:V ratio			
Area of white elevation, study eye	98	−0.34	0.0006
Area of white elevation, fellow eye	109	−0.07	0.46
Area of total elevation, study eye	84	−0.25	0.02
Area of total elevation, fellow eye	87	−0.02	0.84
Frisén grade, study eye	98	−0.24	0.02
Frisén grade, fellow eye	109	−0.19	0.05
PMD, study eye	98	−0.06	0.58
PMD, fellow eye	109	0.08	0.39

Associations (Spearman rank correlations) among features assessed in both study eye and the fellow eye and selected variables.

assess papilledema using the Frisén scale, with equal or greater consistency than was achieved by independent expert reviewers.

Recently, Echegaray et al.¹⁵ described an automated analysis of optic nerve images based on a vessel discontinuity index, measures of disc boundary obscuration, and mean entropy of the retinal nerve fiber layer. Although there was excellent discrimination for Frisén grades 0, 1, and 2, there was somewhat less sensitivity in discriminating grades 3 and 4. No grade 5 images were included in the dataset, which was also sparse for grades 3 and 4. The observed loss of sensitivity is consistent with our observation that vessel continuity is highly dependent on camera focus, justifying the protocol requirement of obtaining two sets of disc photographs at different focal planes.

Interpretation of Results

We demonstrated strong correlations between Frisén grade and the areas of “white” and “total” elevation of the optic nerve head (Spearman correlations of 0.65–0.72, $P < 0.0001$). This degree of association is remarkable given that Frisén grading is highly dependent on the identification of vascular discontinuity over the disc, whereas the area of disc elevation is independent of vascular assessment. Possibly the discontinuity in the retinal vessels over the disc indicates the height of the papilledema, not considered in the two-dimensional analyses performed in this study.

We found that the Frisén grade was weakly, but statistically significantly correlated with opening pressure on lumbar puncture (Spearman correlations of 0.28–0.31, $P < 0.0002$), whereas the areas of “white” elevation and “total” elevation were more weakly associated with opening CSF pressure. One possible explanation is that the translucence of the edematous

tissue rather than the total area of disc elevation is more reflective of intracranial pressure. Tang et al.¹² reconstructed disc volume from stereoscopic fundus photographs, showing a reasonable association ($r^2 = 0.6$) with OCT reconstructions of optic disc volume, a technique that may be helpful in better understanding the divergence between disc area and Frisén grade. Optical coherence tomography disc volumes are evaluated directly in an IIHTT substudy reported separately.^{16,17}

Sinclair et al.¹⁰ suggested that blood vessel diameter changes with severity of papilledema. Moss et al.¹⁸ demonstrated that manual and semiautomated techniques could be used to measure vascular changes on scanning laser ophthalmoscopy. In a small number of subjects, they found that vein diameter was increased in subjects with papilledema compared with healthy subjects or those with pseudo-papilledema, whereas arterial diameter did not differ among the groups. Furthermore, they showed that vein diameter decreased after treatment for and resolution of papilledema. Although we failed to find consistent evidence of associations between papilledema measures and either venous or arterial diameters, we believe that the internal control for arterial diameter provided by computing the A:V ratio resulted in stronger relationships, as shown in Figure 8.

STUDY LIMITATIONS

Equipment

The original concern of adequate image sensor resolution proved to be less of an issue than the limited dynamic range of many older sensors. The inability of older sensors to image the highly reflective disc and the darker retina led to a loss of detail and uncertainty in both Frisén grading and quantitative assessment. The model eye provided excellent magnification calibration for each camera system. Theoretically, the standardized colors incorporated in the model should have allowed for color correction and color matching between sites. Color correction using the color checker in the eye model was unachievable due to unauthorized interim changes in sensor color settings and wide exposure variations that occurred at the sites.

Grading

Although we were able to confirm that trained lay readers were as reliable as experts in the Frisén grading process, the limitations of subjective, qualitative interpretations of disc edema remain. Nonetheless, photographic documentation is critical for the preservation of clinical findings for future studies, including the validation and usefulness of new technology such as OCT. The quantitative assessment of the retinal and optic disc photographs was time-consuming, and we are not certain of its utility in clinical practice.

Summary

The certification of photographic equipment combined with the training of photographic technicians as well as lay readers led to reliable, high-quality imaging data acquisition and analysis within the context of a multicenter, prospective clinical trial. Measures of disc edema were not significantly associated with PMD, the principal outcome measure used in the IIHTT. Frisén grades were highly correlated with the area of disc edema, moderately correlated with CSF pressure, and weakly correlated with A:V ratio.

FIGURE 8. The graphs show the associations between the A:V ratio and the area of “total” elevation (a), area of “white” elevation (b), and the Frisén grade (c).

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References

- Friedman DI. Pseudotumor cerebri. *Neurol Clin.* 2004;22:99-131, vi.
- Corbett JJ, Savino PJ, Thompson HS, et al. Visual loss in pseudotumor cerebri. Follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss. *Arch Neurol.* 1982;39:461-474.
- NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee, Wall M, McDermott MP, et al. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. *JAMA.* 2014;311:1641-1651.
- Hubbard LD, Danis RP, Neider MW, et al. Brightness, contrast, and color balance of digital versus film retinal images in the age-related eye disease study 2. *Invest Ophthalmol Vis Sci.* 2008;49:3269-3282.
- Bull L. Color management for ophthalmic fundus photography. *J Ophthalmic Photogr.* 2009;31:40.
- Danis RP, Domalpally A, Chew EY, et al. Methods and reproducibility of grading optimized digital color fundus photographs in the age-related eye disease study 2 (AREDS2 report number 2). *Invest Ophthalmol Vis Sci.* 2013;54:4548-4554.
- Bengtsson B, Krakau CE. Correction of optic disc measurements on fundus photographs. *Graefes Arch Clin Exp Ophthalmol.* 1992;230(1):24-28.
- Scott CJ, Kardon RH, Lee AG, et al. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. *Arch Ophthalmol.* 2010;128:705-711.
- Frisén L. Swelling of the optic nerve head: a staging scheme. *J Neurol Neurosurg Psychiatry.* 1982;45:13-18.
- Sinclair AJ, Burdon MA, Nightingale PG, et al. Rating papilloedema: an evaluation of the Frisén classification in idiopathic intracranial hypertension. *J Neurol.* 2012;259:1406-1412.
- Wang JK, Kardon RH, Kupersmith MJ, et al. Automated quantification of volumetric optic disc swelling in papilledema using spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2012;53:4069-4075.
- Tang L, Kardon RH, Wang JK, et al. Quantitative evaluation of papilledema from stereoscopic color fundus photographs. *Invest Ophthalmol Vis Sci.* 2012;53:4490-4497.
- Trick GL, Vesti E, Tawansy K, et al. Quantitative evaluation of papilledema in pseudotumor cerebri. *Invest Ophthalmol Vis Sci.* 1998;39:1964-1971.
- Wall M, Kupersmith MJ, Kiebertz KD, et al. The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. *JAMA Neurol.* 2014;71:693-701.
- Echegaray S, Zamora G, Yu H, et al. Automated analysis of optic nerve images for detection and staging of papilledema. *Invest Ophthalmol Vis Sci.* 2011;52:7470-7478.
- OCT Sub-Study Committee for the NORDIC Idiopathic Intracranial Hypertension Study Group. Baseline OCT measurements in the idiopathic intracranial hypertension treatment trial: part I. Quality control, comparisons and variability. *Invest Ophthalmol Vis Sci.* 2014;55:8180-8188.
- OCT Sub-Study Committee for the NORDIC Idiopathic Intracranial Hypertension Study Group. Baseline OCT measurements in the idiopathic intracranial hypertension treatment trial: part I. Correlations and relationship to clinical features. *Invest Ophthalmol Vis Sci.* 2014;55:8173-8179.
- Moss HE, Treadwell G, Wanek J, et al. Retinal vessel diameter assessment in papilledema by semi-automated analysis of SLO images: feasibility and reliability. *Invest Ophthalmol Vis Sci.* 2014;55:2049-2054.

APPENDIX

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