

Original Investigation

The Idiopathic Intracranial Hypertension Treatment Trial Clinical Profile at Baseline

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IMPORTANCE To our knowledge, there are no large prospective cohorts of untreated patients with idiopathic intracranial hypertension (IIH) to characterize the disease.

OBJECTIVE To report the baseline clinical and laboratory features of patients enrolled in the Idiopathic Intracranial Hypertension Treatment Trial.

DESIGN, SETTING, AND PARTICIPANTS We collected data at baseline from questionnaires, examinations, automated perimetry, and fundus photography grading. Patients (n = 165) were enrolled from March 17, 2010, to November 27, 2012, at 38 academic and private practice sites in North America. All participants met the modified Dandy criteria for IIH and had a perimetric mean deviation between -2 dB and -7 dB. All but 4 participants were women.

MAIN OUTCOMES AND MEASURES Baseline and laboratory characteristics.

RESULTS The mean (SD) age of our patients was 29.0 (7.4) years and 4 (2.4%) were men. The average (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) was 39.9 (8.3). Headache was the most common symptom (84%). Transient visual obscurations occurred in 68% of patients, back pain in 53%, and pulse synchronous tinnitus in 52%. Only 32% reported visual loss. The average (SD) perimetric mean deviation in the worst eye was -3.5 (1.1) dB, (range, -2.0 to -6.4 dB) and in the best eye was -2.3 (1.1) dB (range, -5.2 to 0.8 dB). A partial arcuate visual field defect with an enlarged blind spot was the most common perimetric finding. Visual acuity was 85 letters or better (20/20) in 71% of the worst eyes and 77% of the best eyes. Quality of life measures, including the National Eye Institute Visual Function Questionnaire-25 and the Short Form-36 physical and mental health summary scales, were lower compared with population norms.

CONCLUSIONS AND RELEVANCE The Idiopathic Intracranial Hypertension Treatment Trial represents the largest prospectively analyzed cohort of untreated patients with IIH. Our data show that IIH is almost exclusively a disease of obese young women. Patients with IIH with mild visual loss have typical symptoms, may have mild acuity loss, and have visual field defects, with predominantly arcuate loss and enlarged blind spots that require formal perimetry for detection.

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Idiopathic intracranial hypertension (IIH) is a syndrome characterized by increased intracranial pressure, with its associated signs and symptoms, in an alert and oriented patient. Neuroimaging is normal except for findings known to occur with chronic increased intracranial pressure of any cause. Lumbar puncture and cerebrospinal fluid (CSF) analysis findings were normal except for increased intracranial pressure. In addition, no secondary cause of intracranial hypertension is apparent (modified Dandy criteria for IIH, eBox 1 in Supplement).¹

Idiopathic intracranial hypertension occurs with a frequency of about 1 case per 100 000 population per year or 19.3 per 100 000 in obese women aged 20 to 44 years,² and its incidence has increased in concert with the obesity epidemic. Loss of sensory visual function, occurring in most patients,³ is the only major morbidity associated with IIH. Because about 10% of patients develop bilateral blindness,^{3,4} having evidence-based treatment strategies is important.

Treatment of the condition is based on anecdotal uncontrolled data because there are no properly designed and executed clinical trials to guide therapy.⁵ With this in mind, investigators of the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Study Group developed the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a multicenter, double-blind, randomized, placebo-controlled study of 165 patients with mild visual loss; our range of mild visual loss comprises a subset of about one-third of patients with IIH. All patients received a lifestyle modification program of weight reduction with a low-sodium diet. Additionally, patients were randomized to receive either acetazolamide or matching placebo. Here, we report the baseline clinical and laboratory features of enrolled IIHTT patients; trial results will be published in another article.⁶

Methods

The study was approved by each site's institutional review board and written informed consent was obtained from patients. The tenets of the Declaration of Helsinki were followed. One hundred sixty-five patients with IIH with mild visual loss were enrolled at 38 NORDIC sites in the United States and Canada over a 3-year period. Patients were included if they met the modified Dandy criteria for IIH (eBox 1 in the Supplement) and had perimetric mean deviation (PMD) between -2 and -7 dB on 24-2 SITA (Swedish interactive thresholding algorithm) Standard testing that was reproducible; -2 dB was chosen so that patients would have room to improve and -7 dB was chosen because some investigators believed surgical treatments were necessary for those with more severe visual loss. eBox 2 in the Supplement outlines the major eligibility criteria for the IIHTT.

Patients were randomly assigned to receive a supervised low-sodium diet either with acetazolamide or with matching placebo. A specific dietary plan and lifestyle modification intervention was offered to all study participants with a study weight loss counselor provided by the New York Obesity and Nutrition Research Center. The target weight-loss goal at 6 months was 6% loss of total body weight.

The study drug was acetazolamide, 250 mg, or matching placebo tablets. The initial dosage of study drug was 4 tablets

daily in 2 divided doses followed by dosage increases of 1 tablet every week up to a maximum dosage of 4 g daily. We chose this maximum dosage because increasing dosages of acetazolamide with concomitant intracranial pressure monitoring showed gradual CSF pressure reduction once patients reached a dosage of 4 g per day.⁷ The dosage titration was stopped if the participant's papilledema grade (Frisén scale)^{8,9} became less than 1 in both eyes and the PMD improved to equal to or better than -1 dB in each eye, unless the presence of other symptoms, such as headache or pulse synchronous tinnitus, suggested that the dosage titration continue. Patients who were unable to tolerate the study drug could gradually decrease the dosage to a minimum of one-half tablet daily. Patients who discontinued the study drug continued to be followed up, if willing, for the planned 6-month duration.

Treatment failure was defined when a patient with baseline PMD up to -3.5 dB had visual function worsen by more than 2 dB PMD from baseline in either eye or when a patient with baseline PMD between -3.5 dB and -7 dB had visual function worsen by more than 3 dB PMD from baseline in either eye, confirmed by a second perimetric examination. Using all available clinical information, an adjudication committee needed to decide whether the worsening was most likely due to uncontrolled intracranial pressure and progression of IIH. Patients who experienced treatment failure were withdrawn from further participation in the trial.

Outcome variables were assessed at baseline and at follow-up visits, with end-of-study assessments (6 months) being of primary interest. The primary outcome variable was the change from baseline to 6 months in the PMD of the eye with the worst PMD at baseline.

Questionnaires

Historical data relevant to IIH were captured at each visit. To assess vision-related quality of life, the National Eye Institute Visual Function Questionnaire-25 (VFQ-25),^{10,11} the 10-item Neuro-Ophthalmic Supplement to the VFQ-25,¹² and Version 2 of the Short Form-36 Health Survey¹³ were administered. For the evaluation of headache, we administered the Headache Impact Test-6 inventory.

Baseline Evaluation

Each patient had general medical, ophthalmologic, and neurologic history and examination; magnetic resonance imaging; blood for genetic analysis and other research laboratory investigations; and a lumbar puncture. A best-corrected visual acuity using trial lenses mounted in spectacles was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. The Berlin Questionnaire was given to assess sleep apnea risk (patients with known, untreated obstructive sleep apnea were excluded from participation).

Perimetry

Patients underwent automated perimetry using the Humphrey Field Analyzer SITA Standard program 24-2 in both eyes. The testing was performed by a certified technician using the IIHTT manual of procedures for the Visual Field Reading Center (VFRC). Each patient had at least 2 initial visual field ex-

aminations done at least 1 hour apart. The average of the 2 PMDs of the visual field examinations that best met criteria for entry was used as the baseline value. The eye with the worst PMD was considered the study eye. Visual field defects were categorized by 3 VFRC readers. The results of the categorization of the second visual field are reported.

Fundus Photography

The papilledema grade (Frisén scale)^{8,9} was documented at each visit by the site investigator and by the Photographic Reading Center for photographs centered on the optic disc focused at the retinal plane, on the plane of highest disc elevation, and in the papillomacular area.

Obesity Evaluation

Height, weight, and waist circumference were measured at each study visit. Further details regarding the methods of the trial are provided in a separate article.¹⁴

Statistical Analyses

The analyses were largely descriptive, with means, standard deviations, and ranges reported for continuous variables and counts and percentages reported for categorical variables. Associations between continuous variables are described using either Pearson correlation coefficients or Spearman rank correlation coefficients, as appropriate.

Results

Demographics

Of the 317 people (308 women and 9 men) interested in participating, 152 (147 women and 5 men) failed screening and 165 (161 women and 4 men) were enrolled. There were 152 patients who were classified as screen failures. The reasons for failure are given in eTable 1 in Supplement. The average (SD) age of enrollees was 29.0 (7.4) years (range, 18-52 years). Five percent of the enrolled patients identified family members with IIH. Sixty-five percent were white, 25% were black, and 10% reported another race/ethnicity or did not report a race/ethnicity.

Obesity Evaluation

The mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) was 39.9 (8.3) (range, 24.9-71.2). Recent weight change history and waist circumference data are found in eTable 2 in Supplement.

Symptoms Reported at Study Entry

The most common initial symptom was headache; other initial symptoms are reported in Figure 1A. Headache was also the most common baseline symptom overall (84%). Transient visual obscurations occurred in 68% of patients; the median number was 1 per day (range, 1 per month to 25 per day). Pulse synchronous tinnitus occurred in 52% of patients; it was bilateral in two-thirds of cases and unilateral in one-third. It occurred an average (SD) of 16.7 (12.3) days per month, ranging from once monthly to daily. Tinnitus that was nonpulsatile was present in 23%; in one-third of these patients, the tinnitus occurred daily.

Back pain, including pain in a radicular pattern, occurred in 53%. Double vision was reported by 18% of patients. The prevalence of other baseline symptoms is found in Figure 1B.

Headache

On a scale of 0 to 10, the average (SD) headache severity was 6.3 (1.9), with 9 patients (5.4%) reporting a severity of 10. In 51% of those reporting headache, the headache was either constant or daily. For those with intermittent headache, the median number of days per month with headache was 12 (range, 1-30 days). The average (SD) Headache Impact Test score was 59.7 (9.0) (range, 36-78). Forty-one percent reported a premorbid history of migraine (17% had migraine with aura).

Signs

Data on arterial blood pressure and intraocular pressure are found in eTable 3 in Supplement. The average (SD) PMD in the study (worst) eye was -3.5 (1.1) dB; results for the best eye were -2.3 (1.1) (range, -5.2 to 0.8 dB). Figure 2 depicts the distributions of PMD results. The average (SD) PMD difference between eyes was 1.3 (0.9) dB (range, 0-5.2 dB).

The VFRC readers classified defects by superior and inferior hemifields because glaucomalike nerve fiber bundle type damage occurs in IIH.⁴ They found that 80.6% of the superior hemifields in the study eye and 86.1% of the inferior hemifields had nerve fiber bundle type visual field loss; 59.4% of the superior hemifields and 64.8% of the inferior hemifields of the fellow eye had this type of loss. The most prominent baseline hemifield abnormality classification was a partial arcuate defect with an enlarged blind spot (about three-fourths of the hemifields in the study eye and about half of the hemifields in the fellow eye; Figure 3; eTable 4 in Supplement). The frequencies of other visual field defects are found in eTable 4 in Supplement.

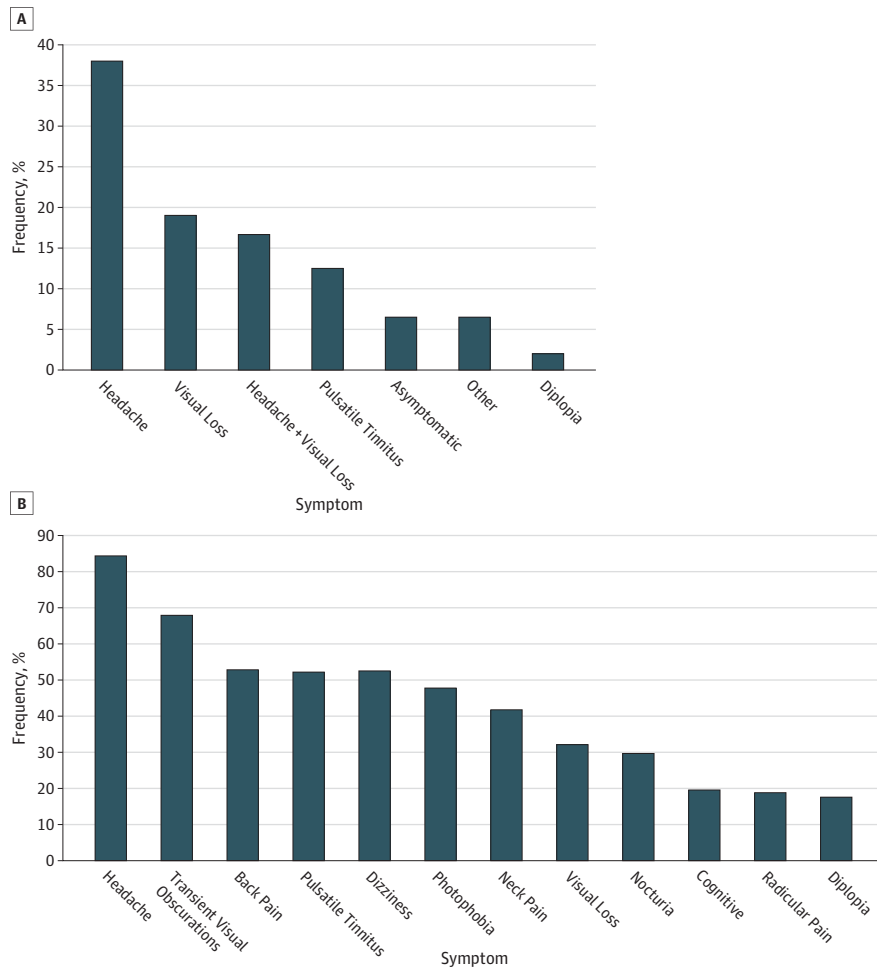
Visual acuity was measured by the ETDRS method, with a score of 85 being equivalent to visual acuity of 20/20. Visual acuity was 85 letters or better in 70.9% of the study eyes and 77.0% of the fellow eyes (Figure 4, eTable 5 in Supplement). Visual acuity was 20/25 or worse in 24% of study eyes and 27% of nonstudy eyes; it was 20/32 or worse in 9% of study eyes and 10% of nonstudy eyes (eTable 5 in Supplement). There was no significant relationship between ETDRS score and PMD in the study eye.

Papilledema grading using the Frisén scale was done separately by the Photographic Reading Center using the study photographs and the site investigator using clinical ophthalmoscopy. Study entry required a grade of at least 1 by the Photographic Reading Center. Grade 2 was the most common finding (Figure 5). There was no discernible relationship between PMD and papilledema grade in the study eye (Spearman correlation = 0.01, $P = .91$). Twelve patients (7%) had asymmetric papilledema defined as a 2-grade or more difference.

A relative afferent pupillary defect was found in 5.4% of eyes. While binocular diplopia was reported in 18%, only 3% had an esotropia on examination, suggesting the presence of sixth nerve palsy; this is best explained by the diplopia likely being transient.

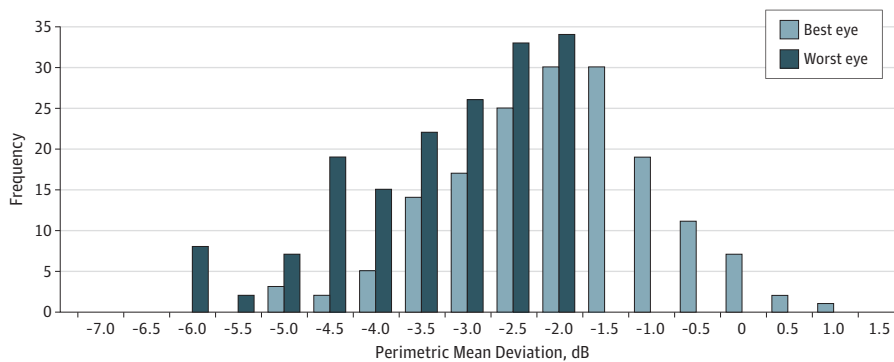
The average (SD) CSF opening pressure, obtained using a standardized lumbar puncture protocol, was 343.5 (86.9) mm H₂O (range, 210-670 mm H₂O). There was no significant relationship between body mass index and CSF pressure (Pear-

Figure 1. Symptoms



A, Graph shows initial symptoms reported at study entry. Other initial symptoms were floaters, dizziness, and nonpulse synchronous tinnitus. B, Graph shows the frequency of all symptoms reported at study entry.

Figure 2. Histogram of Mean Deviation Values of Idiopathic Intracranial Hypertension Treatment Trial Patients at Baseline



A perimetric mean deviation of -2 to -7 dB was required for entry.

son correlation = 0.28, $P = .08$). There was also no statistically significant relationship between CSF pressure and PMD (CSF pressure = $-5.82 \times \text{PMD} + 323.0$; $r^2 = 0.006$; $P = .34$).

Sixty-four percent of patients had a risk score of 2 or 3 on the Berlin Questionnaire, putting them at high risk for sleep apnea.¹⁵

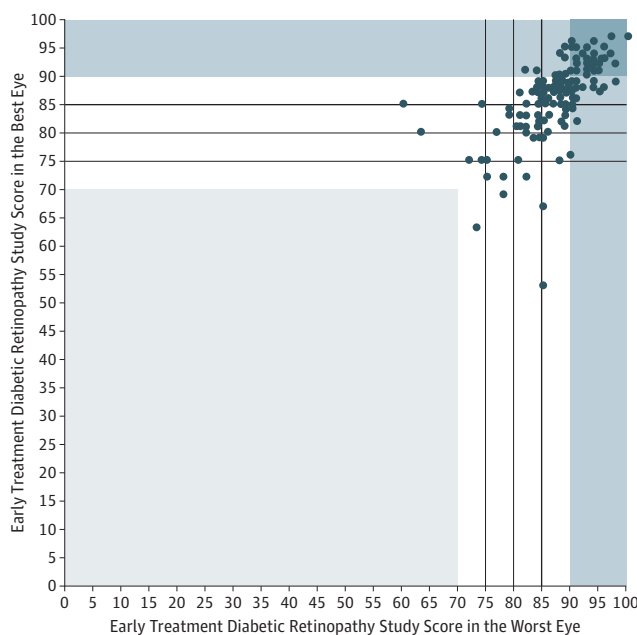
At baseline, the mean (SD) total score on the National Eye Institute VFQ-25 was 82.4 (15.1) (range, 20.2-100), with higher scores representing better vision-related quality of life. Our cohort's 10-item supplement scores had an average (SD) of 75.4 (14.5) (median, 77; range, 26-100). The average (SD) Short Form-36 physical health summary score was 45.8 (9.0) (range,

Figure 3. A Typical Example of the Most Common Visual Field Defect



Images show an enlarged blind spot with a partial inferior arcuate nerve fiber bundle defect.

Figure 4. Early Treatment Diabetic Retinopathy Study Score of the Worst Eye Plotted Against That for the Best Eye at Study Entry



Dark shaded areas indicate vision of 20/15 or better. The light shading indicates 20/40 vision or worse. The bold grid lines at the score of 85 are equivalent to 20/20; at 80 are 20/25; and at 75 are 20/32.

16.8-62.0); the mean score for women aged 25 to 34 years in the United States was 53, with higher scores representing better quality of life. The average (SD) mental health summary score was 44.6 (12.6) (range, 7.0-63.9), with the mean¹³ for US women aged 25 to 34 years of 48.

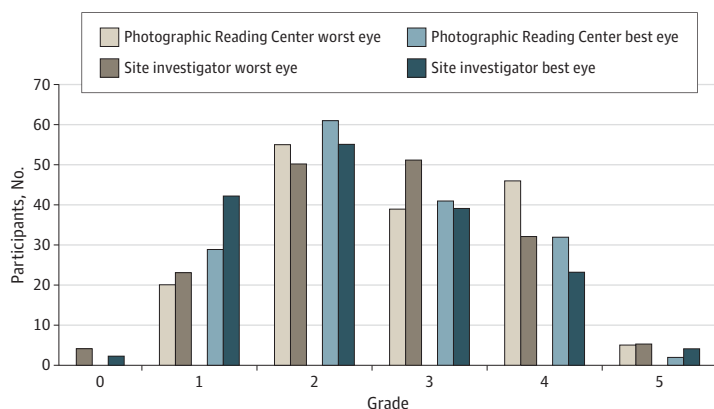
Discussion

Our cohort consisted almost exclusively of women (98%). While many large IIIH series report a preponderance of women, usually in the 90% range,^{3,4,16-18} to our knowledge, this is the largest percentage of women in a major series. Although it is possible that women are more likely to enter clinical trials, there is evidence to the contrary.¹⁹ Our high percentage of women

compared with other trials may be owing to the strict adherence to both the modified Dandy criteria for IIIH and the eligibility criteria that screened out patients with secondary causes of intracranial hypertension. This high percentage raises the possibility that IIIH may be a disease of women and most men may have other disorders such as sleep apnea-related intracranial hypertension.

Five percent of patients identified family members with IIIH. Because all of our patients were overweight and 88% were obese and because obesity is also inherited, it is possible that simply inheriting genes related to obesity increases the risk for IIIH. This does not explain the low frequency of IIIH in the general population or the female preponderance. Furthermore, the results of a survey for papilledema at an obesity clinic²⁰ using optic disc photographs of 606 patients revealed only 2 partici-

Figure 5. Frisén Papilledema Grading



Grade 1 by the Photographic Reading Center was required for study entry.

pants with papilledema, which does not support a simple relationship with obesity. Because papilledema in an obese population is rare, our rate of 5% of patients with a family history of IIH suggests a genetic basis for IIH.

Symptoms in our patients were similar in frequency and type to those found in other prospective studies.^{3,4,21} Headache was the most common initial symptom in our patients (84%) as in other studies.^{3,4,22,23} In about half of IIHTT participants reporting headache, the headache was constant or daily. This supports considering IIH as a cause of new daily persistent headache in the appropriate demographic. A prior prospective study³ revealed headaches to be usually daily pulsatile pains that gradually increased in intensity with nausea. The reduced Headache Impact Test-6 mean score we found was consistent with substantial headache-related disability over the preceding month.^{24,25}

Johnston and Paterson²⁶ observed no clear relationship between changes in intracranial pressure and headache presence. And experimentally induced increased intracranial pressure in humans produced inconsistent headache responses.²⁷ The mechanism of headache in IIH is further clouded by the common co-occurrence of medication overuse (rebound) headache.²⁸

Transient visual obscurations (TVOs) are transient episodes of visual loss that usually last less than 30 seconds, occur in 1 or both eyes, and are followed by full visual recovery. Transient visual obscurations occurred in 68% of our IIHTT patients—similar to the 72% found by others.^{3,4} Transient visual obscurations are not specific for IIH²⁹ and are not associated with the extent of disc edema.^{3,30} Sadun et al³¹ noted the occurrence of TVO in other conditions and proposed transient ischemia of the optic nerve head due to increased local tissue pressure as the likely etiology. Having TVOs was not related to the amount of vision loss at presentation and does not appear to be associated with a poor visual outcome.³

Pulse synchronous tinnitus, also called *pulsatile tinnitus*, was reported by 52% of IIHTT patients. It was usually bilateral and was noticed about once every 2 days. Pulsatile tinnitus was found in 60% of patients with IIH in a consecutive prospective series of 50 patients.³ Sismanis³² found pulsatile tinnitus in each of 20 patients with IIH. Low-frequency hearing loss occurred in 18 of his 20 patients and improved with therapy. Temporary

improvement of the intracranial sound occurred with digital pressure over the ipsilateral jugular vein. Pulsatile tinnitus may be due to the turbulent flow through the functional venous stenoses of the transverse sinus that are common in IIH.³³

Radicular pain, including neck and shoulder and pain in a radicular or dermatomal pattern, was common in our patients (Figure 1B). The mechanism of this symptom is thought to be filling of spinal dural root sheaths by CSF under high pressure.³⁴

Signs of IIH are primarily related to the loss of afferent visual function. While most of the damage in the visual field is peripheral, subtle or mild degrees of central loss is found.³⁵ Given that the IIHTT entry criteria required mild visual field loss in the worse (study) eye, our perimetric results are not representative of visual loss in IIH in general.

Visual acuity is assumed to remain normal in patients with IIH except in cases with severe visual loss or when there is a neurosensory detachment in the papillomacular region. In our patients, the ETDRS visual acuity score (number of letters correct) was 85 letters (20/20 equivalent) or better in only 70.9% of study eyes at baseline and 77.0% of the fellow eyes (Figure 3). This is unexpected given the mild degree of visual field loss and indicates more acuity loss than what has been reported.^{3,36,37} This is especially noteworthy given the population norm for this age group is visual acuity of 20/15.³⁸ To our knowledge, this is the first IIH study that has used a standardized refraction protocol and the ETDRS score for visual acuity outcome. It is not clear whether this acuity loss is due to a neurosensory detachment, choroidal folds, or optic nerve damage.

Ophthalmoscopic examination and fundus photography failed to reveal a relationship between PMD and papilledema grade in the worst eye. However, the small 5-dB PMD range may have masked this relationship that has been reported.³⁹ Highly asymmetric papilledema (2 Frisén grade or more difference) was found in 7%. This is similar to the previously reported 10%.³⁵

We used PMD as a measure of global visual field loss because it is a summary of the average visual field loss per test location, with slightly more weight given to the more centrally placed thresholds. The average (SD) PMD in the worst eye at baseline was -3.5 (1.1) dB. The average PMD for the other eye was about 1 dB less. The VFRC classification revealed that most of the hemifields had abnormalities in the study eye consist-

ing of nerve fiber bundle type visual loss. This took the form of enlarged blind spots and arcuate defects. Blind spot enlargement is ubiquitous but, because refraction with additional plus lenses can eliminate this defect,⁴⁰ we did not consider this significant visual loss unless it encroached on fixation. Retinal mechanisms of visual loss are neurosensory detachments and choroidal folds.⁴¹ The latter cause cecentral defects that can be reduced with the addition of plus lens at the perimeter. However, most visual loss in IIH is due to damage at the optic nerve head. It is thought that high CSF pressure is reflected along the arachnoid trabeculations of the optic nerve sheath, causing a high-pressure gradient across the optic nerve head. There is resultant axoplasmic flow stasis; intra-axonal swelling; and compression of axons, capillaries, and small arterioles, resulting in ischemic damage to the optic disc.⁴²

Obstructive sleep apnea risk was found to be high in our IIH cohort based on the Berlin Questionnaire scores. Thurtell and colleagues⁴³ found a similar rate of risk (67%). In this study, polysomnography showed that 18 of 20 high-risk patients, via the Berlin Questionnaire, had sleep apnea based on an apnea-hypopnea index of greater than 5.

The National Eye Institute VFQ-25 scores were decreased. Daniels and colleagues⁴⁴ reported quality of life results from a case-control study of 34 patients with newly diagnosed IIH; their mean VFQ-25 scores were significantly lower than those

observed either in neuro-ophthalmologic control individuals or in disease-free control cases. The lower scores in our IIHTT patients were similar to those of the neuro-ophthalmologic control individuals in the study by Daniels et al⁴⁴; this may be owing to our entry criteria requiring mild visual loss. Kleinschmidt et al⁴⁵ also reported decreased quality of life in patients with IIH using the Short Form-36.

Conclusions

To our knowledge, our study has yielded the largest set of prospectively collected data in IIH. We found the highest percentage of women reported to date in both our enrolled and screened patients. These data confirm that the clinical profile of IIH in patients with mild visual loss is that of a young overweight woman in the third and fourth decades with headache, back pain, transient visual obscurations, pulse synchronous tinnitus, papilledema, and visual loss. The diagnosis of IIH should be made with caution in nonobese patients, men, and those without typical symptoms such as headache, transient visual obscurations, and pulse synchronous tinnitus. Our study does not speak to the clinical profile of IIH in those with moderate to severe visual loss; evidence-based treatments of these patients await future randomized clinical trials.

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