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# Research Submissions

## Headache in Idiopathic Intracranial Hypertension: Findings From the Idiopathic Intracranial Hypertension Treatment Trial

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**Objective.—To characterize the phenotype, headache-related disability, medical co-morbidities, use of symptomatic headache medications, and headache response to study interventions in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).**

**Methods.—Patients with untreated IIH and mild vision loss enrolled in the IIHTT and randomized to acetazolamide (ACZ) and weight loss or placebo (PLB) and weight loss had prospective assessment of headache disability using the Headache Impact Test-6 (HIT-6) questionnaire. Subjects with headache at the baseline visit were assigned a headache phenotype using the International Classification for Headache Disorders version 3 beta (ICHD-3b). Medication overuse was determined using the participants' reported medication use for the preceding month and ICHD-3b thresholds for diagnosing medication overuse headache. We investigated relationships between headache disability and various other clinical characteristics at baseline and at 6 months.**

**Results.—Headache was present in 139 (84%) of the 165 enrollees at baseline. The most common headache phenotypes were migraine (52%), tension-type headache (22%), probable migraine (16%), and probable tension-type headache (4%). Fifty-one (37%) participants overused symptomatic medications at baseline, most frequently simple analgesics. A similar amount of improvement in the adjusted mean (± standard error) HIT-6 score occurred in the ACZ (–9.56 ± 1.05) and PLB groups (–9.11 ± 1.14) at 6 months (group difference −0.45, 95% CI −3.50 to 2.60, $P = .77$). Headache disability did not correlate with any of the studies, variables of interest, which included: the lumbar puncture opening pressure at baseline or at 6 months, body mass index, the amount of weight lost, papilledema grade, perimetric mean deviation, or the use of hormonal contraception. Headache disability was significantly associated with patient-reported quality of life in the physical, mental, and visual domains.**

**Conclusions.—Headache was common, of varied character, disabling, and associated with poorer quality of life in our cohort of patients with mild visual impairment. The lack of correlation between headache disability and cerebrospinal fluid (CSF) pressure at baseline and at the end of the randomized phase of the study implies that headache in IIH may be related to factors other than intracranial hypertension, and that specific headache treatment is needed in addition to therapies directed at lowering CSF pressure.**

**Key words: idiopathic intracranial hypertension, headache, medication overuse, Headache Impact Test-6**

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## INTRODUCTION

Headache is the most common presenting symptom in idiopathic intracranial hypertension (IIH), reported in over 90% of patients.[1-3] IIH is in the differential diagnosis of new daily persistent headache, as well as in patients developing new headaches or experiencing a change in a previously established headache pattern. Based on consensus opinion, the International Classification of Headache Disorders version 3 beta (ICHD-3b) diagnostic criteria for headache attributed to IIH do not specify a particular headache phenotype but require at least two of the following characteristics in a patient with a diagnosis of IIH and a documented lumbar puncture opening pressure of $\geq$250 mm of water: (1) the headache developed in temporal relation to IIH, or led to its discovery, (2) headache is relieved by reducing intracranial hypertension, and (3) headache is aggravated in temporal relation to an increase in intracranial pressure.[4]

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) prospectively studied 165 participants with newly-diagnosed IIH and mild visual loss, representing the largest research cohort of patients with IIH to date. Regarding headache in IIH, our aims were to (1) report the effect of acetazolamide on headache disability in a setting where all subjects received a dietary management intervention, (2) characterize the headache phenotype of participants at study entry, (3) determine whether headache disability correlated with visual function (perimetric mean deviation [PMD]), the severity of papilledema (Frisén grade), body mass index (BMI), and standardized quality of life (QoL) measurements at baseline and at 6 months, (4) investigate whether initiation of headache prophylactic treatment during the study improved headache disability and the number of headache days at 6 months, and (5) assess whether the use of hormonal contraception or the presence of co-morbidities associated with migraine were associated with the development or severity of headaches. Herein, we report the aspects of the IIHTT related to headache including phenotypes, headache-related disability, medical co-morbidities, and response to treatment during the course of the study.

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## METHODS

The IIHTT was approved by the institutional review board at each site and written informed consent was obtained from each participant. The trial was registered on clinicaltrials.gov (NCT01003639). One hundred sixty-five participants between ages 18 and 60 years with recently diagnosed IIH and mild visual loss (PMD $-2$ to $-7$ dB) were enrolled at 38 study sites in the United States and Canada from March 2010 to November 2012.[5,6] All participants had papilledema at the time of study entry. Details of how the diagnosis of IIH was made as well as detailed study inclusion and exclusion criteria have been previously published.[5] Enrollees, including 161 women and 4 men, were randomized to receive either acetazolamide or placebo in a standardized, gradually escalating dosage over a 2-month period.[6] The starting dosage was 500 mg BID of acetazolamide or matching placebo tablets, with a maximum dosage of 2 g BID. All participants had access to a supervised medical weight reduction program and were provided education to follow a low sodium diet. The primary outcome variable was the change from baseline to Month 6 in PMD. Details of the protocol and study results may be found elsewhere.[5,6]

Enrollees were queried about headache at baseline and at subsequent visits at 1, 2, 3, 4.5, and 6 months. The standardized questionnaire inquired about the location of the head pain, headache frequency (chronic or intermittent; number of headaches during the preceding month at baseline; number of headache days per month thereafter), headache character, associated symptoms (photophobia, phonophobia, nausea, vomiting, aggravation by routine physical activity), severity (0-10 scale), and the presence of neck, back, or eye pain. Medications used to treat headaches were compiled in detail, and participants were specifically asked

about the use of over-the-counter medications and opioids. Participants indicated whether or not their headaches had caused them to miss work, school, or social activities. All participants completed the Headache Impact Test-6 (HIT-6) questionnaire at each visit.[6] The HIT-6 was selected because it has a 1-month recall and was recommended by focus groups of patients with IIH as being the most straightforward questionnaire asking relevant questions about IIH-related headaches.

Headache phenotype was determined by a manual review of each participant's headache symptoms and classified using the items in the ICHD-3b that characterize the headache: criteria C and D for migraine without aura (1.1) and criteria B and C for tension-type headache (2.1).[4] Headache frequency at baseline was determined from questionnaire responses in which subjects were asked how many headaches they had in the preceding month, and whether their headache was "constant" or "intermittent." Because a headache diary was not available, and subjects were not asked to report the number of headache days at baseline, responses of "constant" frequency on the questionnaire were interpreted as occurring every day and were classified as daily. "Intermittent" frequency responses were interpreted as not occurring every day and were classified as chronic (occurring 15 or more days/month) or episodic (occurring 14 or fewer days per month). The number of headache days was assumed to be the same as the number of days that any symptomatic treatment was used to treat headache.

Medication overuse was defined based on the ICHD-3b criteria for diagnosing medication overuse headache (8.2.3, 8.2.4, 8.2.5). Medications taken for symptomatic and preventive treatment of headache were ascertained by a manual review of each participant's concomitant medication log. Analgesics used transiently for treatment of another condition, such as postoperative pain, nephrolithiasis, back pain or post-lumbar puncture headaches, were not included in the analysis.

In the study protocol, specific medications were recommended to site investigators for headache treatment after study entry. Naproxen, acetaminophen, and ibuprofen were preferred, and acetaminophen with codeine as well as butalbital compound were allowed. Triptans and dihydroergotamine were permitted for co-existing migraines. Site investigators were specifically instructed to limit acute treatment to three times weekly and to prescribe a preventive medication to participants requiring symptomatic medication more than 3 days weekly. Preferred preventive medications were amitriptyline (10-50 mg HS), protriptyline (5-20 mg BID), naproxen (up to 1 g daily in divided doses), and nortriptyline (up to 25 mg HS) with the caveat that close monitoring for weight gain was required when amitriptyline or nortriptyline were used. Second-tier recommendations were gabapentin (100 mg HS to 400 mg TID) and fluoxetine (20 mg daily). All study participants were offered the same medications. Topiramate was not allowed during the double-masked phase of the trial and had to be discontinued at least 7 days before the baseline visit. Corticosteroids could not be prescribed during the study period.

General health-related QoL was assessed using the Short Form-36 (SF-36) and vision-related QoL was measured using the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) and neuro-ophthalmic supplement at baseline and at 6 months.[6]

**Statistical Analysis.—**All analyses were specified after the conclusion of the IIHTT but were not suggested by the data. Sample size and power considerations were based on the primary aims of the IIHTT[5] and not on the aims of the secondary analyses reported here. Group comparisons with respect to HIT-6 total score were performed using two-sample *t*-tests. Group comparisons of proportions were performed using chi-square tests. Bivariate associations between variables were assessed using Spearman rank correlation coefficients. Logistic regression analyses were performed separately to determine the associations between each of 3 baseline variables (papilledema grade in the worst eye [1-3 vs 4-5], BMI, and cerebrospinal fluid [CSF] opening pressure) and the development of headache after baseline in those with no headache at baseline. A significance level of 5% (two-tailed)

**Table 1.—Headache Phenotype at Baseline**

| | | No MO | MO – Simple | MO – Other |
|---|---|---|---|---|
| MIGRAINE | Daily | 0 | 13 | 6 |
| N=72 | Chronic | 11 | 7 | 3 |
| | Episodic | 31 | 0 | 1 |
| PROBABLE | Daily | 3 | 1 | 1 |
| MIGRAINE | Chronic | 0 | 3 | 0 |
| N=22 | Episodic | 13 | 0 | 1 |
| TENSION-TYPE | Daily | 0 | 4 | 2 |
| N=30 | Chronic | 5 | 1 | 0 |
| | Episodic | 18 | 0 | 0 |
| PROBABLE | Daily | 0 | 0 | 0 |
| TENSION-TYPE | Chronic | 1 | 1 | 0 |
| N=5 | Episodic | 3 | 0 | 0 |
| UNCLASSIFIED | Daily | 0 | 4 | 1 |
| N=10 | Chronic | 0 | 2 | 0 |
| | Episodic | 3 | 0 | 0 |

Daily = occurring every day; Chronic = 15 or more headache days/month; Episodic = 14 or fewer headache days/month. MO = medication overuse; Simple = simple analgesics; Other = opioids or caffeine-containing analgesics.

was used for hypothesis testing and no adjustments were performed for multiple testing. All analyses were performed using SAS software, Version 9.3.

## RESULTS

**Baseline.—**One hundred thirty-nine participants (84%) had headaches at baseline, 70 in the acetazolamide group, and 69 in the placebo group. Headache was the initial symptom of IIH in 35%. Thirty-eight enrollees (22 in the acetazolamide group and 16 in the placebo group) had either chronic or daily headaches at baseline, as determined by the number of days they took analgesics for relief.

The headache phenotypes described were migraine (n = 72, 52%), probable migraine (n = 22, 16%), tension-type headache (n = 30, 22%), and probable tension-type headache (n = 5, 4%) (Table 1). The headaches could not be classified in 10 participants (7%). The character of the head pain was pressure-like 47% and throbbing in 42%. The location of pain was frontal in 68%, global in 36%, posterior in 39%, unilateral in 30%, ocular in 47%, and nuchal in 47%. Associated symptoms included photophobia (70%), phonophobia (52%), nausea (47%), vomiting (17%), and worsening with routine physical activity (50%). Participants with headache also experienced the IIH-related symptoms of constant visual loss (34%), transient visual obscurations (68%), diplopia (22%), and dizziness (53%). Twenty individuals in the study (14%) had headache without constant visual loss, transient visual obscurations, diplopia, or dizziness. Nine participants (5%) reported having photophobia without headache. Twenty-three percent of enrollees described constant (daily) pain with an overall median frequency of 12 headache days monthly.

Mean (± standard deviation) headache severity at baseline, assessed on a 0-10 rating scale, was 6.3 ± 1.9. The scoring range for the HIT-6 questionnaire is 36-78. The mean HIT-6 score at baseline was 59.7 ± 9.0, indicating substantial to severe impact and was similar in the two treatment groups (acetazolamide: 60.3 ± 8.7; placebo: 59.1 ± 9.3). Mean HIT-6 scores were significantly different for those with (62.1 ± 7.0, n = 96) and without photophobia (56.3 ± 10.4, n = 68, $P < .0001$) and with (62.0 ± 7.6, n = 72) and without phonophobia (57.9 ± 9.6, n = 92, $P = .003$). There were highly significant correlations between the HIT-6 score and NEI-VFQ-25 total score ($r = -0.47$, $P < .0001$) and NEI-VFQ-25 neuro-ophthalmic supplement total score ($r = -0.41$, $P < .0001$) at baseline.[7] The HIT-6 score was also associated with worse QoL on the SF-36 physical ($r = -0.57$, $P < .0001$) and mental ($r = -0.34$, $P < .0001$) component summaries as well as all SF-36 subscale scores (Table 2). Additionally, there was a significant difference in the mean NEI-VFQ-25 total score between those with and without neck pain (group difference = −9.39, $P = .001$).[7]

Participants commonly used symptomatic headache treatment prior to their baseline evaluation, often more than one medication per person. Simple analgesics reported at the baseline visit were ibuprofen (n = 54), acetaminophen (n = 23), naproxen (n = 13), aspirin (n = 2), and ketorolac (n = 1). Combination analgesic medications included aspirin/acetaminophen/caffeine (n = 15), butalbital-containing compounds (n = 4), and isometheptene

**Table 2.—Spearman Correlations With Headache Outcomes**

| | HIT-6 Total Score | | Number of Headache Days | |
|---|---|---|---|---|
| | *r* | *P* Value | *r* | *P* Value |
| Papilledema grade in worst eye | 0.01 | .89 | 0.14 | .13 |
| PMD in worst eye | −0.02 | .79 | 0.03 | .78 |
| CSF opening pressure | 0.06 | .43 | 0.23 | .04 |
| Body mass index | −0.03 | .68 | −0.03 | .74 |
| SF-36 | | | | |
| Physical Component Summary | −0.57 | <.0001 | −0.51 | <.0001 |
| Mental Component Summary | −0.34 | <.0001 | −0.20 | .03 |
| Physical functioning subscale | −0.42 | <.0001 | −0.33 | .0002 |
| Role-physical subscale | −0.53 | <.0001 | −0.38 | <.0001 |
| Bodily pain subscale | −0.54 | <.0001 | −0.50 | <.0001 |
| General health subscale | −0.35 | <.0001 | −0.32 | .0004 |
| Vitality subscale | −0.54 | <.0001 | −0.37 | <.0001 |
| Social functioning subscale | −0.47 | <.0001 | −0.29 | .001 |
| Role-emotional subscale | −0.26 | .0008 | −0.22 | .02 |
| Mental health subscale | −0.34 | <.0001 | −0.21 | .02 |
| NEI-VFQ-25 total score | −0.47 | <.0001 | −0.46 | <.0001 |
| NEI-VFQ-25 10-item neuro-ophthalmic supplement | −0.41 | <.0001 | −0.31 | .0005 |

PMD = perimetric mean deviation; CSF = cerebrospinal fluid.
Correlations with HIT-6 total score are computed using data from the baseline visit; correlations with the number of headache days are computed using data from the Month 6 visit because the number of headache days was not collected at baseline.

(n = 1). Five individuals took hydrocodone, five used tramadol, two took acetaminophen with codeine, and one used butalbital with codeine. Fifty-one participants (37%) were overusing symptomatic pain medications prior to enrollment (Table 1). Fifteen of them met criteria for overusing opioids/combination medications and the others overused simple analgesics. Three participants reported using oral triptans for migraine treatment. Mean HIT-6 score was significantly higher in those with medication overuse (63.1 ± 6.9) than in those without medication overuse (58.1 ± 9.4; $P = .0007$).

There was no correlation between the HIT-6 score and either CSF opening pressure ($r = 0.06$, $P = .43$) or BMI ($r = -0.03$, $P = .68$). Similarly, the mean CSF opening pressure did not differ significantly between those with (348.1 ± 82.2 mm water) and without (331.9 ± 90.9 mm water) headache ($P = .37$), and there was no significant difference in mean BMI in participants who did (39.8 ± 8.3) and did not (39.9 ± 8.3) have daily headaches ($P = .98$). There were no significant correlations between HIT-6 score and papilledema grade, PMD, or BMI (Table 2).

*Headache History and Co-Morbidities.*—Of the 94 participants with a headache phenotype of migraine or probable migraine at baseline, 47 (50%) had a prior history of migraine with or without aura. Of the 45 participants with non-migrainous headaches at baseline, 13 (29%) related a history of migraine. Hormonal contraception use was not associated with the presence of headache; 31 of 37 (84%) participants using hormonal contraception and 108 of 128 (84%) not using hormonal contraception experienced headaches ($P = .93$). Hormonal contraception use was likewise not associated with HIT-6 score, with mean scores being 59.9 ± 8.9 in users and 59.6 ± 9.0 in non-users ($P = .90$).

Other medical conditions reported at baseline for the entire study cohort included depression (n = 39), anxiety (n = 31), polycystic ovarian

**Table 3.—HIT-6 Scores at Baseline and Six Months by Treatment Group**

| | | Placebo | Acetazolamide |
|---|---|---|---|
| | | N (%) | N (%) |
| Baseline | Overall | 79 | 85 |
| | Little to no impact | 11 (14%) | 9 (11%) |
| | Some impact | 15 (19%) | 14 (16%) |
| | Substantial impact | 8 (10%) | 11 (13%) |
| | Severe impact | 45 (57%) | 51 (60%) |
| 6 Months | Overall | 56 | 66 |
| | Little to no impact | 25 (45%) | 27 (41%) |
| | Some impact | 12 (21%) | 18 (27%) |
| | Substantial impact | 6 (11%) | 15 (23%) |
| | Severe impact | 13 (23%) | 6 (9%) |

(The difference in patient numbers from Baseline to 6 Months is due to participant withdrawal from the trial.)

syndrome (n = 28), thyroid disease (n = 6), bipolar disorder (n = 4), sleep apnea (n = 7), and high risk for sleep apnea as determined by the Berlin Questionnaire (n = 106). There was no significant difference between those with and without any of these conditions with respect to mean HIT-6 scores except that those with a high risk of sleep apnea had a higher mean HIT-6 score (60.8 ± 9.2) than those with a low risk of sleep apnea (57.7 ± 8.3, $P = .04$).

**Six Months.—**As reported in the primary publication of the IIHTT,[5] 69% of the participants in the acetazolamide group and 68% of participants in the placebo group reported having headaches at Month 6 (odds ratio [OR] 1.10, 95% CI 0.53 to 2.28, $P = .80$). Headache disability improved in both treatment groups between baseline and 6 months (mean change in HIT-6 score −9.56 in the acetazolamide group vs −9.11 in the placebo group), and the group difference (–0.45, 95% CI −3.50 to 2.60, $P = .77$) was not significant. For all participants, the mean HIT-6 score at 6 months was 51.2 ± 9.1 (acetazolamide group 50.8 ± 8.8, placebo group 51.5 ± 9.4), indicating some impact on the ability to function. Of those who had HIT-6 scores available at Month 6, a similar percentage of participants in each treatment group (acetazolamide: 32%; placebo: 34%) indicated that their headaches had a substantial or severe impact on their lives (Table 3). There was no correlation between the HIT-6 score at Month 6 and the maximum dosage of study drug taken in the acetazolamide group ($r = -0.09$, $P = .48$).

Twenty-one enrollees did not have headache at baseline but reported headache at one or more follow-up visits. Neither baseline CSF opening pressure (OR 0.997, 95% confidence interval [CI] 0.991 to 1.003, $P = .32$), baseline papilledema grade (OR 1.88, 95% CI 0.74 to 4.81, $P = .19$), nor BMI at baseline (OR 1.02, 95% CI 0.97 to 1.08, $P = .39$) were associated with the subsequent development of headache. Only five participants reported no headache at any time during the 6-month study period; they also did not experience diplopia, visual loss, photophobia, or pulsatile tinnitus.

With regard to medications used to treat headache, preventive therapy with tricyclic antidepressants was prescribed to 16 participants after enrollment (seven in the acetazolamide group and nine in the placebo group) and data were available for 12 of them at 6 months. Two of the remaining four participants met study criteria for treatment failure, and two withdrew consent. The mean

**Table 4.—Key Points**

1 Headache was a common symptom and caused significant disability, contributing to poor general and visual quality of life.
2 While headache tended to improve overall in the IIHTT, there was no difference in headache outcomes between the acetazolamide and placebo groups at 6 months. A substantial proportion of participants had severe headaches at 6 months, stressing the importance of incorporating other headache treatments.
3 There was no association between headache presence, intensity, or degree of disability and CSF pressure at baseline, and only a small correlation with headache disability and CSF pressure at 6 months.
4 Medication overuse was frequent in this population at baseline.
5 Prior history of migraine was very high in IIH patients at 41% vs 18% in the general population.
6 80% of patients with headache had symptoms not normally associated with migraine or tension-type headache.
7 There was neither significant weight gain nor ICP elevation in the small cohort of patients using tricyclic antidepressants to treat headache.

change in HIT-6 score from baseline to 6 months in this group was $-5.2 \pm 9.0$, which was slightly less in magnitude than the mean change in the total study cohort. The mean change in weight in this group at Month 6 from Baseline was $-7.7 \pm 6.8$ kg, which was statistically significant ($P = .002$) and comparable to the mean change in weight in the total study cohort (–6.1 ± 6.9 kg).

Only four participants in the IIHTT were overusing analgesics at 6 months (as compared with 51 at baseline). Three of these four were overusing analgesics at baseline; none of the four took preventive medication for headache during the study.

Eighty-five participants (52%) agreed to have a lumbar puncture at 6 months; of those, 65 had headache and 20 did not. There was no correlation between the HIT-6 score and CSF opening pressure ($r = 0.12$, $P = .29$) at 6 months, but the number of headache days correlated weakly with CSF opening pressure ($r = 0.23$, $P = .04$; Table 2). The mean CSF opening pressure was higher in those with headache ($284.1 \pm 87.0$ mm water) than in those without ($231.7 \pm 104.7$ mm water, $P = .03$).

There was no significant correlation between the amount of weight lost and the improvement in HIT-6 score at 6 months ($r = 0.02$, $P = .80$). The NEI-VFQ-25 total score and neuro-ophthalmic supplement total score, the SF-36 physical and mental component summaries, and the SF-36 subscale scores were significantly correlated with the number of headache days at 6 months (Table 2).

## DISCUSSION

Headache was the most common symptom of IIH in this prospective study of participants with mild visual loss and was often the initial symptom; the prominence of this finding is concordant with several prior reports.[3,8,9] Both providers and patients often perceive the headache of IIH as being directly linked to CSF pressure elevation, and they anticipate that lowering CSF pressure will improve headache control. Indeed, the ICHD-3b includes headache improvement or worsening with CSF pressure reduction or elevation, respectively, in the criteria for IIH-related headache.[4] Our prospective data collection showed no correlation between HIT-6 scores and CSF opening pressure at baseline or at 6 months. The ICHD-3b was derived from expert consensus using available evidence. Our findings provide the first class I evidence that CSF pressure and headaches are clinically independent features of IIH. Additionally, there was no significant difference in mean CSF opening pressure between patients with and without headache at baseline, and mean BMI was similar in patients with and without daily headache at baseline as well. During the masked treatment phase of the IIHTT, mean CSF pressure decreased from baseline to 6 months in both the acetazolamide- and placebo-treated groups, although a 59.9 mm $H_2O$ greater mean reduction was seen with acetazolamide (–112.3 vs $-52.4$ mm $H_2O$; $P = .002$).[5] Nonetheless, there was still no statistically significant correlation between the HIT-6 score and the CSF pressure measurement by lumbar puncture at 6 months.

The lack of association between headache presence or intensity and CSF opening pressure at IIH diagnosis has not been reported previously. It is possible that this finding is a result of natural fluctuations in CSF pressure throughout the day, and others have also noted dissociation between headaches and CSF pressure measurements.[10] Many IIH patients have persistent headache despite normalized intracranial pressure.[11] A recent prospective study similarly found that 57% of patients with IIH had sustained, long-term headache despite resolution of papilledema.[12] Likewise, studies of CSF shunting for IIH elated headaches confirm the notion that long-term headache control is frequently independent of CSF pressure management with a 50% headache recurrence rate in 3 years.[13] Elevated CSF pressure might lead to persistent and chronic trigeminal activation and irritation that persists even if intracranial pressure is normalized. This trigeminal dysfunction also could result in chronic dysregulation of normal mechanisms that suppress inappropriate trigeminal nociceptive activity, similar to migraine headache.[14] Thus, the increased overall headache incidence in our cohort is higher than expected in an age and sex-matched population[15] but is not directly related to CSF pressure levels either acutely or long-term.

Headache characteristics in this study were similar to those of patients in other, albeit smaller, published IIH cohort studies. A recent study looking at the applicability of the ICHD-3b criteria found that 84% of IIH patients had focal or unilateral headaches, 52% had pulsatile pain, and a majority of patients had aggravation with cough or Valsalva maneuvers.[16] A series of prospective studies of patients with IIH have reported contradictory headache characteristics including daily or near-daily headache, diffuse/non-pulsating pain, aggravation with Valsalva maneuvers, unilateral pain, and migraine-associated symptoms[9] as well as pulsatile pain and no aggravation with Valsalva.[1,3] These findings illustrate the varied headache qualities among patients with IIH at presentation. Additionally, headaches in IIH patients have many features that overlap with primary headaches. Migrainous features of photophobia and phonophobia, as well as neck stiffness and arm pain, have been described.[17]

The headache phenotype in the IIHTT was heterogeneous with 94 of 139 participants (68%) having a definite or probable migraine phenotype at study entry, and 35 (25%) having headache characteristics similar to definite or probable tension-type headaches. Although there were no specific features of the headache to suggest a diagnosis of IIH, 80% of the patients with headache in our cohort had other symptoms (ie, constant or transient visual loss, diplopia, dizziness) that are not typically experienced with migraine or tension-type headache and would raise the possibility of a secondary cause. However, 20% of those participants with headache at baseline had none of these symptoms. While none of the participants in the IIHTT were asymptomatic at presentation, nine enrollees experienced photophobia in the absence of headache, eight had only back pain, three had only neck pain, and five had back and neck pain without headache. These findings emphasize the importance of a fundoscopic examination to look for papilledema in the evaluation of patients with headache or when IIH is suspected based on other symptoms, particularly in obese women of childbearing age.

To our knowledge, the IIHTT is the first study to assess headache disability in IIH using a validated rating scale. The mean HIT-6 score at baseline was $59.7 \pm 9.0$, indicating substantial to severe impact. The headache impact improved during the 6 months of randomized treatment to $51.2 \pm 9.1$, with similar improvement in both treatment groups. Headache disability in our participants appeared to be a major contributing factor to their reported QoL, as the HIT-6 score was significantly associated with both the physical and mental component summaries of the SF-36, every SF-36 subscale score, the NEI-VFQ-25 total score, and the NEI-VFQ-25 neuro-ophthalmic supplement total score at baseline (Table 2); similar findings have been previously reported.[7] The number of headache days at 6 months was also correlated with these measures of QoL (Table 2).

While headache disability improved in both treatment groups in the IIHTT, neither acetazolamide therapy, the maximum dosage of acetazolamide taken, nor the degree of weight loss were associated with the number of headache days or the HIT-6 score at the end of the randomized treatment phase. These data support the view that additional treatments beyond those used to lower intracranial pressure are needed to treat the headaches associated with IIH.

The most frequently used headache preventive medications in the IIHTT were amitriptyline and nortriptyline. The mean HIT-6 score in participants treated with a tricyclic antidepressant was improved at 6 months, but this improvement was not greater than that in the overall IIHTT cohort. It is unknown whether the participants who received preventive treatment for headaches would have fared worse had they not been treated. Treatment with a tricyclic antidepressant did not appear to have an adverse effect on weight loss.

One-third of participants with headaches at baseline were overusing symptomatic medications. By Month 6, only four participants were overusing analgesics. This decrease may have been a result of education, improvement in headaches reducing the need for acute therapy, or both.

Sixty-seven of the 165 participants in the trial (41%) had a history of migraine, which is much higher than expected in the general population in

whom migraine affects 20% of women and 9% of men.[15] Among women aged 18-44, who comprise the demographic most commonly affected by IIH, the 3-month prevalence of migraine is 23.5%,[15] and incidence of all headaches including migraine appears to be even higher in obese patients.[18] We recognize that IIHTT participants may not be comparable to the general population given the higher rate of obesity and fear of losing vision. Half of the enrollees whose IIH-related headaches had a migraine phenotype had experienced migraines previously. Although migraine has never been implicated as an independent risk factor for developing IIH, the high prevalence of migraine in this cohort raises the possibility that previous episodes of central sensitization related to migraine may contribute to the development of IIH in combination with other features, such as obesity and weight gain. Alternatively, persistent trigeminal dysregulation from intracranial pressure elevation (concurrent or previous) noted above might lower the migraine threshold in patients with and without a prior migraine history.[14]

There are potential limitations of our study. Headache phenotype was ascertained by response to a symptom questionnaire rather than a structured personal interview. The history of migraine and other relevant medical co-morbidities was recorded based on patient report and not otherwise verified. Enrollees did not maintain a headache calendar, as it was felt to be too burdensome to ensure adherence in an effort-intensive and time-consuming study. Thus, there may have been recall bias related to the number of headache days and headache-related disability assessments. We inadvertently queried about the number of headaches, rather than headache days, in the 30 days prior to the baseline visit, and had to infer the number of headache days based, in part, on the number of days that symptomatic treatment was used. This methodology may underestimate the number of headache days at baseline as participants may have experienced intermittent headaches that they did not treat. In particular, we were unable to determine the number of participants with daily headaches in enrollees who did not report taking any symptomatic treatment for their headaches at baseline unless they described their headache as constant.

It is important to note that the complete criteria for each headache diagnosis in the ICHD-3b specify that another ICHD-3b diagnosis has been excluded; we used only the criteria defining the headache phenotype as all of our enrollees had IIH. Additionally, the ICHD-3b criteria for diagnosing medication overuse headache require that symptomatic medications be overused for 3 months. As patients in our cohort were enrolled shortly after being diagnosed with IIH, and the information regarding analgesic use was gathered retrospectively, we queried only about medication use in the 30 days prior to the baseline visit to reduce recall bias. Because we do not have data regarding symptomatic treatment for 3 months, we describe "medication overuse" rather than a diagnosis of "medication overuse headache."

The cohort studied in the IIHTT included only individuals with mild visual field loss and may not be representative of IIH patients with better or worse vision.

In summary, headaches were common and the resulting disability was significant for participants in the IIHTT (Table 4). As there was no correlation between headache disability and CSF pressure at baseline or at 6 months, we recommend that the requirement for headache improvement with CSF pressure reduction be eliminated from the ICHD-3b criteria 7.1.1 (headache attributed to idiopathic intracranial hypertension).[4] Furthermore, we would consider adding to the comments that migraine and other headache types may co-exist and be exacerbated by elevated intracranial pressure. One-third of participants overused symptomatic headache treatments at study entry, emphasizing the need for patient education regarding medication overuse headache. Headache appeared to be a major contributing factor to decreased QoL in physical, mental, and visual domains. While headache frequency and disability improved during the randomized phase of the trial, acetazolamide conferred no greater benefit for headache treatment than did placebo, when combined with a supervised weight reduction, low sodium diet. Tricyclic antidepressants

did not preclude successful weight loss, although the small number of participants taking them for headache prevention and the absence of a randomized control group precludes assessment of their effectiveness. In the absence of any contraindications, we would suggest that migraine prophylactic treatment be considered in all IIH patients with headache, as it has the potential to improve their overall QoL. Data from the longitudinal follow-up study of this cohort may provide further insights into the prognosis of headaches associated with IIH.

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