

Quality of life in idiopathic intracranial hypertension at diagnosis

IIH Treatment Trial results

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ABSTRACT

Objective: The study purpose was to examine vision-specific and overall health-related quality of life (QOL) at baseline in Idiopathic Intracranial Hypertension Treatment Trial patients who were newly diagnosed and had mild visual loss. We also sought to determine the associations between vision-specific QOL scores and visual symptoms, visual function, pain, headache-related disability, and obesity.

Methods: We assessed QOL using the 36-Item Short Form Health Survey, National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25), and 10-Item NEI-VFQ-25 Neuro-Ophthalmic Supplement. We compared these results with those of previously reported idiopathic intracranial hypertension (IIH) QOL studies. We assessed relationships between QOL and other clinical characteristics.

Results: Among 165 participants with IIH (161 women and 4 men with a mean age \pm SD of 29.2 ± 7.5 years), vision-specific QOL scores were reduced compared with published values for disease-free controls. Scores of participants were comparable to published results for patients with multiple sclerosis and a history of optic neuritis. A multiple linear regression model for the NEI-VFQ-25 composite score found that perimetric mean deviation in the best eye, visual acuity in the worst eye, visual symptoms, and pain symptoms (headache, neck pain), but not obesity, were independently associated with QOL.

Conclusions: IIH affects QOL at time of diagnosis even in patients with mild visual impairment. Vision-specific QOL in patients with newly diagnosed IIH may be as decreased as that for patients with other neuro-ophthalmic disorders. IIH treatment should target visual loss and other symptoms of increased intracranial pressure associated with reduced QOL. Reduced QOL does not simply reflect obesity, an underlying IIH risk factor. *Neurology*® 2015;84:2449-2456

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **HIT-6** = 6-item Headache Impact Test; **IIH** = idiopathic intracranial hypertension; **IIHTT** = Idiopathic Intracranial Hypertension Treatment Trial; **MS** = multiple sclerosis; **NEI-VFQ-25** = National Eye Institute Visual Function Questionnaire-25; **NORDIC** = Neuro-Ophthalmology Research Disease Investigator Consortium; **PMD** = perimetric mean deviation; **QOL** = quality of life; **SF-36** = 36-Item Short Form Health Survey.

Idiopathic intracranial hypertension (IIH) is characterized by an elevation of intracranial pressure of uncertain etiology. Once termed “benign intracranial hypertension,” case series subsequently showed that some patients may have devastating long-term visual consequences, emphasizing that outcomes of this condition may not always be favorable.¹ Other frequently associated symptoms, including headache, pulse synchronous tinnitus, back and neck pain, and photophobia, also may affect quality of life (QOL).² Initial investigations showed reduced QOL in women with IIH^{3,4} and have generated a need for better characterization of IIH-associated morbidity. Assessment of QOL yields a measure for evaluating treatment options.

Supplemental data
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NORDIC Idiopathic Intracranial Hypertension Study Group coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

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Previous studies examined QOL in IIH. A retrospective cross-sectional analysis of patients with IIH demonstrated poor overall health-related QOL, measured by the 36-Item Short Form Health Survey (SF-36), when compared with obese and normal weight controls. Furthermore, patients with IIH had increased depression and fatigue.³ A prospective controlled study of women within 6 months of IIH diagnosis showed decreased QOL, as measured by the SF-36 and the 25-Item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), relative to other neuro-ophthalmic conditions.⁴

The IIH Treatment Trial (IIHTT) is the first study to prospectively assess QOL of patients with mild visual loss at the time of diagnosis. The purpose of this paper is to report vision-specific and overall health-related QOL at baseline in IIHTT participants. We also sought to determine associations between vision-specific and overall QOL scores and visual function, symptoms, headache-related disability, and obesity in this cohort.

METHODS Patients. This study was a cross-sectional evaluation of baseline QOL characteristics of participants with IIH and mild visual loss enrolled in the IIHTT, a randomized, double-masked, placebo-controlled trial of acetazolamide. All participants received a low-sodium, weight-reduction diet. To be eligible for the study, participants satisfied the Modified Dandy Criteria for IIH⁵ and had baseline computerized automated perimetric mean deviation (PMD) between -2 and -7 dB in the worst affected eye on a 24-2 SITA standard test (Humphrey; Carl Zeiss Meditec, Inc., Dublin, CA). All participants were enrolled within 4 weeks of IIH diagnosis. At the screening visit, the site coordinator explained the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Web site and opened an account to give the participant the option of completing the QOL assessments and other self-reported questionnaires online. Study team members took a complete medical history at each participant's screening visit and reviewed it at the baseline visit. They also collected baseline self-reported change in weight over the previous 6 months, weight, standing height, and body mass index (BMI) data.

Other visual function testing. A certified technician measured high-contrast visual acuity using retroilluminated Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Lighthouse International Low Vision Products, New York, NY). The technician also tested low-contrast letter acuity using retroilluminated, low-contrast Sloan letter charts (Precision Vision, La Salle, IL) at 2.5% and 1.25% contrast levels. Study team members performed an ocular examination, pupillary testing, and direct and indirect ophthalmoscopic evaluations at the screening and baseline visits. The site investigator and the Photographic Reading Center graded papilledema for each eye using the Frisén Scale.^{6,7}

QOL assessments. We administered QOL questionnaires at the baseline visit. Participants completed the questionnaires on the NORDIC Web site up to 1 week before baseline, or completed the questionnaires during the baseline visit. Vision-specific QOL was assessed with the NEI-VFQ-25.^{8,9} This self-administered scale includes 25 questions with response gradings that use a Likert scale. Assessment also included administering the more recently designed (Raphael 2006) 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25.⁹ The SF-36 measured overall health-related QOL.¹⁰ Each patient also completed the 6-item Headache Impact Test (HIT-6) questionnaire¹¹ to evaluate headache disability and the Berlin Sleep Apnea Questionnaire to discern the possibility of underlying sleep apnea, which would exclude the patient from participating. The present report includes only the baseline data from the IIHTT. One participant's baseline NEI-VFQ-25, Neuro-Ophthalmic Supplement, and SF-36 were unavailable/incomplete, as was the Neuro-Ophthalmic Supplement for 2 other participants.

Standard protocol approvals, registrations, and patient consents. We conducted this study in accordance with the Declaration of Helsinki. The institutional review board at each site approved this study, and all participants provided written informed consent.

Statistical analysis. Statistical analyses used R 3.0.3 (The R Foundation for Statistical Computing, <http://www.r-project.org>). Linear regression models examined the associations between QOL scores (NEI-VFQ-25, Neuro-Ophthalmic Supplement, and SF-36 Physical and Mental Component Summaries) and, separately, each of 35 participant characteristics: age, race, sex, BMI, years of education, current and longest class of occupation, years in current and longest class of occupation, marital status, visual acuity in each eye, PMD in each eye, Frisén papilledema grade in each eye, CSF opening pressure, symptoms of back pain, neck pain, binocular diplopia, cognitive dysfunction, dizziness/vertigo, nocturia, photophobia, radicular pain, pulsatile tinnitus, nonpulsatile tinnitus, subjective visual change for the worse, constant visual loss, transient visual obscurations, history of migraine, amblyopia in either eye, and recent weight gain, and HIT-6 score and high-risk Berlin questionnaire score. Additional univariate models evaluated each subscale of the 4 QOL scales as outcome variables. Robust (sandwich) variance estimates determined confidence intervals (CIs) and p values due to heteroscedasticity (i.e., nonconstant variance of the residuals from the fitted regression model).¹² The investigators considered all variables in the univariate analyses for inclusion in a multiple linear regression model, and they used an all subsets approach to select models for consideration based on Mallows C_p ¹³ and the Bayesian information criterion.¹⁴

RESULTS Demographics. One hundred sixty-one women and 4 men met all eligibility criteria and enrolled in the trial.¹⁵⁻¹⁷ Table 1 lists participant characteristics and corresponding characteristics of cohorts from other studies. The age range was 18 to 52 years. Most participants (65%) self-identified as white/Caucasian while 25% were African American, 2% were Native American, and 8% were of other races or did not report their race; also, 13% were Hispanic/Latino. A BMI >30 kg/m², indicating obesity, was present in 88% of patients.

Table 1 Baseline characteristics for IIHTT participants (n = 165) and comparison with cohorts from other published studies of IIH

	IIHTT cohort, ¹⁶ 2014	Daniels et al., ⁴ 2007	Kleinschmidt et al., ³ 2000
Study design	Randomized, double-masked, placebo-controlled clinical trial	Case-control study with prospective ascertainment	Case-control study with retrospective ascertainment
Controls in study	Not applicable	Patients with other neuro-ophthalmologic disorders at tertiary care centers, category-matched for age and sex	Healthy age- and weight-matched
Sample size, n	165	34	28
Age, y, mean ± SD	29.2 ± 7.5	32 ± 10	33 ± 7
Sex	Women, n = 161 (98%); men, n = 4 (2%)	Women, n = 34 (100%)	Women, n = 28 (100%)
Time from IIH diagnosis to study entry, median (range)	All were entered within 2 mo of diagnostic MRI and not treated with drug for more than 2 wk	5.1 mo (0.5-57)	55 mo (0-204)
Time from LP to completion of QOL measures	Mean 8.7 d, median 7 d	Not known	Not known
BMI, kg/m², mean ± SD or median (range)	39.9 ± 8.3 (24.9-71.2)	31.8 (20-70)	37.4 ± 7.0
Headache, % reporting symptom	84	Not captured	78
Depression, % reporting symptom	Not captured	33 (by self-report)	68 (by Beck Depression Inventory scores)
Sleep difficulties	64% at risk of sleep apnea (by Berlin Sleep Questionnaire)	Not captured	82% (by self-report)

Abbreviations: BMI = body mass index; IIH = idiopathic intracranial hypertension; IIHTT = Idiopathic Intracranial Hypertension Treatment Trial; LP = lumbar puncture; QOL = quality of life.

The mean educational level was 14.0 ± 3.1 years; number of years of education was greater among patients with higher (better) NEI-VFQ-25 composite scores (table 2). Sex (male–female = -10.24 points; 95% CI: $-28.93, 8.45$; $p = 0.28$), age (-0.01 points per year; 95% CI: $-0.31, 0.29$; $p = 0.96$), race (black–white = 0.23 points; 95% CI: $-5.17, 5.62$; $p = 0.93$), ethnicity (Hispanic/Latino–not Hispanic/Latino = -3.91 ; 95% CI: $-10.08, 2.26$; $p = 0.21$), and BMI (0.18 points per kg/m^2 ; 95% CI: $-0.12, 0.47$; $p = 0.24$) were not associated with NEI-VFQ-25 composite score.

Symptoms. The most frequent symptoms at study entry were headache in 84% and transient visual obscurations in 68%. Patients also commonly reported tinnitus, both pulsatile (52%) and nonpulsatile (23%), back pain (52%), dizziness (51%), photophobia (48%), neck pain (42%), cognitive dysfunction (21%), and radicular pain (19%). Diplopia was reported in 18%; however, only 3% had an esotropia or sixth nerve palsy documented on the examination.

Headache severity on entry was 6.3 ± 1.9 on a 0 to 10 visual analog scale; only 5.4% reported headache severity of 10/10 on this scale. The majority of patients (51%) indicated that they experienced headache on a daily basis. A substantial proportion (41%) of patients reported a history of migraine. The HIT-6 headache disability score averaged 59.7 ± 9.0 and ranged from 36 to 78 (of a possible 78 as the maximum disability score).

Regarding symptoms, higher HIT-6 score, indicating a greater headache burden, was associated with a lower (worse) NEI-VFQ-25 composite score (figure, table 2). Transient visual obscurations, subjective constant visual loss, dizziness/vertigo, photophobia, neck pain, radicular pain, self-reported cognitive dysfunction, and high risk score on the Berlin Sleep Apnea Questionnaire were significantly associated with a lower NEI-VFQ-25 composite score (table 2). However, there was no significant association between NEI-VFQ-25 composite score and pulsatile tinnitus, nonpulsatile tinnitus, or back pain.

Visual acuity and visual fields. The average PMD in the study eye (worse eye) was -3.5 ± 1.1 dB. In the non-study eye, the PMD was -2.3 ± 1.1 dB. The average visual acuity in the study eye was 86.3 ± 5.5 letters identified correctly on the ETDRS chart; in the non-study eye, the average was 87.3 ± 5.5 ETDRS letters. There was a significant association of PMD in each eye with NEI-VFQ-25 composite score (table 2). Visual acuity (0.35 points per letter in the worst eye; 95% CI: $-0.04, 0.75$; $p = 0.08$; 0.32 points per letter in the best eye; 95% CI: $-0.19, 0.83$; $p = 0.22$) was not associated with NEI-VFQ-25 composite score.

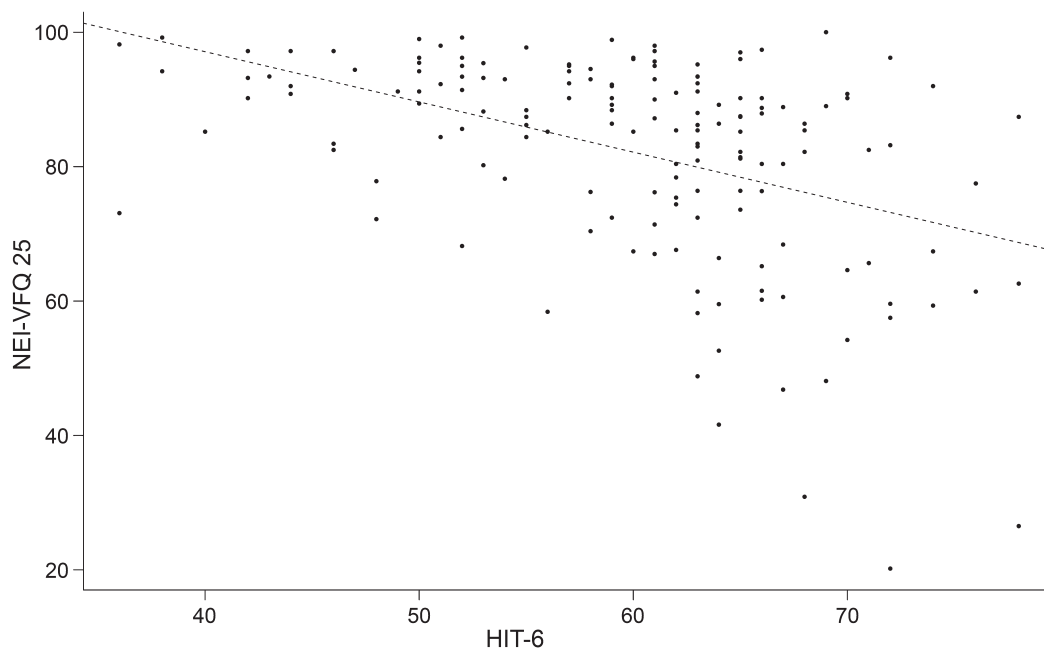
Associations of patient factors with other QOL scores. There were significant associations between the Neuro-Ophthalmic Supplement and self-reported cognitive dysfunction, dizziness/vertigo, neck pain, photophobia, radicular pain, years of education,

Table 2 Factors that showed univariate associations ($p < 0.05$) with one or more of the quality-of-life scales

	NEI-VFQ-25	NEI-VFQ-25 NOS	SF-36 PCS	SF-36 MCS
PMD, worst eye, dB	2.25 (0.01, 4.50); $p = 0.049$	0.92 (-1.06, 2.91); $p = 0.36$	-0.01 (-1.19, 1.16); $p = 0.98$	0.46 (-1.49, 2.42); $p = 0.64$
PMD, best eye, dB	2.72 (0.62, 4.82); $p = 0.01$	1.47 (-0.40, 3.33); $p = 0.12$	0.55 (-0.79, 1.88); $p = 0.42$	0.14 (-1.69, 1.97); $p = 0.88$
Subjective cognitive dysfunction, present-absent	-7.47 (-13.15, -1.80); $p = 0.01$	-8.64 (-14.15, -3.13); $p = 0.002$	-6.16 (-10.11, -2.20); $p = 0.002$	-3.70 (-8.28, 0.89); $p = 0.11$
Dizziness/vertigo, present-absent	-7.01 (-11.46, -2.56); $p = 0.002$	-7.22 (-11.54, -2.89); $p = 0.001$	-4.54 (-7.20, -1.88); $p < 0.001$	-6.43 (-10.13, -2.73); $p < 0.001$
Neck pain, present-absent	-9.39 (-14.03, -4.76); $p < 0.001$	-7.60 (-12.07, -3.13); $p < 0.001$	-1.87 (-4.65, 0.90); $p = 0.19$	-5.01 (-8.85, -1.17); $p = 0.01$
Nocturia, present-absent	-1.74 (-6.74, 3.26); $p = 0.50$	-3.45 (-8.39, 1.49); $p = 0.17$	-3.26 (-6.36, -0.16); $p = 0.04$	0.06 (-4.38, 4.50); $p = 0.98$
Photophobia, present-absent	-7.39 (-11.92, -2.87); $p = 0.001$	-7.42 (-11.77, -3.07); $p < 0.001$	-2.63 (-5.38, 0.11); $p = 0.06$	-4.01 (-7.83, -0.19); $p = 0.04$
Radicular pain, present-absent	-6.76 (-12.75, -0.77); $p = 0.03$	-7.37 (-12.48, -2.27); $p = 0.005$	-7.74 (-11.58, -3.90); $p < 0.001$	-2.49 (-7.49, 2.50); $p = 0.33$
Recent weight gain, present-absent	-2.12 (-6.69, 2.45); $p = 0.36$	0.34 (-4.10, 4.79); $p = 0.88$	-1.68 (-4.42, 1.07); $p = 0.23$	-4.03 (-7.74, -0.32); $p = 0.03$
Years of education, per year	1.18 (0.20, 2.16); $p = 0.02$	0.96 (0.09, 1.82); $p = 0.03$	0.46 (-0.02, 0.95); $p = 0.06$	0.81 (0.15, 1.47); $p = 0.02$
HIT-6, per point	-0.75 (-1.00, -0.50); $p < 0.001$	-0.66 (-0.89, -0.43); $p < 0.001$	-0.58 (-0.72, -0.44); $p < 0.001$	-0.46 (-0.68, -0.24); $p < 0.001$
Berlin score, high risk-low risk	-5.49 (-9.83, -1.14); $p = 0.01$	-3.82 (-8.26, 0.62); $p = 0.09$	-4.87 (-7.46, -2.28); $p < 0.001$	-5.34 (-9.01, -1.67); $p = 0.004$
Pulsatile tinnitus, present-absent	-2.41 (-7.00, 2.17); $p = 0.30$	-5.00 (-9.42, -0.58); $p = 0.03$	0.01 (-2.73, 2.75); $p = 0.99$	-0.57 (-4.42, 3.28); $p = 0.77$
Nonpulsatile tinnitus, present-absent	-4.78 (-10.22, 0.65); $p = 0.08$	-3.32 (-8.31, 1.66); $p = 0.19$	-4.47 (-7.88, -1.07); $p = 0.01$	-0.20 (-4.37, 3.97); $p = 0.93$
Subjective change in vision in either eye, present-absent	-2.98 (-7.80, 1.84); $p = 0.23$	-1.81 (-6.24, 2.62); $p = 0.42$	-2.92 (-5.82, -0.02); $p = 0.048$	-4.11 (-7.95, -0.26); $p = 0.04$
Transient visual obscurations, present-absent	-12.04 (-15.61, -8.46); $p < 0.001$	-10.77 (-14.75, -6.80); $p < 0.001$	-7.00 (-9.47, -4.53); $p < 0.001$	-8.15 (-11.52, -4.78); $p < 0.001$
Subjective constant visual loss, present-absent	-8.52 (-13.86, -3.18); $p = 0.002$	-7.44 (-12.25, -2.62); $p = 0.002$	-0.61 (-3.75, 2.54); $p = 0.71$	-2.73 (-6.98, 1.52); $p = 0.21$
Binocular diplopia, present-absent	-10.49 (-17.17, -3.82); $p = 0.002$	-14.70 (-20.58, -8.82); $p < 0.001$	-3.12 (-6.82, 0.59); $p = 0.10$	-4.22 (-8.87, 0.44); $p = 0.08$

Abbreviations: MCS = Mental Component Summary; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire-25; NOS = Neuro-Ophthalmic Supplement; PCS = Physical Component Summary; PMD = perimetric mean deviation; SF-36 = 36-Item Short Form Health Survey. Results presented are regression coefficients (95% confidence limits).

Figure Baseline NEI-VFQ-25 composite score vs HIT-6 score in IIHTT participants with newly diagnosed IIH



Plot of the NEI-VFQ-25 composite score (y-axis) vs HIT-6 score (x-axis) at baseline in participants with newly diagnosed IIH in the IIHTT. The plot also shows the least-squares regression line. Higher HIT-6 scores, consistent with worse headache disability, were significantly associated with worse NEI-VFQ-25 composite scores (-0.75 per point increase on the HIT-6; 95% confidence interval: $-1.00, -0.50$; $p < 0.001$). HIT-6 = 6-item Headache Impact Test; IIH = idiopathic intracranial hypertension; IIHTT = Idiopathic Intracranial Hypertension Treatment Trial; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire-25.

HIT-6 score, pulsatile tinnitus, transient visual obscurations, and binocular diplopia (table 2). The SF-36 Physical Component Summary score was associated with self-reported cognitive dysfunction, dizziness/vertigo, nocturia, radicular pain, HIT-6 score, high-risk Berlin questionnaire score, nonpulsatile tinnitus, self-reported change in vision for worse in either eye, and transient visual obscurations (table 2). Furthermore, data indicated an association between the SF-36 Mental Component Summary score and dizziness/vertigo, neck pain, photophobia, recent weight gain, years of education, HIT-6 score, high-risk Berlin questionnaire score, self-reported change in vision for worse in either eye, and transient visual obscurations (table 2).

Subscale scores for the NEI-VFQ-25, Neuro-Ophthalmic Supplement, and SF-36 were associated with HIT-6 score and with the presence of transient visual obscurations (table e-1 on the *Neurology*[®] Web site at Neurology.org). The Supplement items that were most affected (lowest mean scores) included difficulty seeing when eyes are tired, feeling that the 2 eyes see differently, and vision being blurry, not clear, or fuzzy (table e-2).

Comparisons with disease-free controls. Study findings indicated a reduction in mean vision-specific QOL (NEI-VFQ-25 composite and Neuro-Ophthalmic

Supplement) scores, as well as mean overall QOL (SF-36) scores (table e-3), compared with those reported for disease-free controls.^{4,9} In addition, the average NEI-VFQ-25 composite score and Neuro-Ophthalmic Supplement score were worse than the scores reported for individuals with multiple sclerosis (MS) and optic neuritis.⁹

Multiple regression models for the NEI-VFQ-25 composite score. A multiple linear regression model with Mallows C_p closest to the number of parameters found that lower PMD in the best eye, worse visual acuity in the worst eye, higher HIT-6 score, presence of neck pain, presence of transient visual obscurations, and presence of binocular diplopia were associated with reduced vision-specific QOL as measured by the NEI-VFQ-25 composite score (table 3). The model with the minimum Bayesian information criterion contained only neck pain, HIT-6 score, transient visual obscurations, and visual acuity in the worst eye. Other similar models variably contained PMD in the best eye or diplopia.

DISCUSSION Study results demonstrate that IIH affects both vision-specific and overall QOL. Compared with published controls and norms, these reductions are substantial even at diagnosis and with only mild visual loss. Reductions in

Table 3 Multiple linear regression model for the NEI-VFQ-25 composite score

Factor	Change in NEI-VFQ-25 (95% CI)	p Value
PMD, best eye, per dB	1.87 (0.16, 3.58)	0.03
VA, worst eye, per letter	0.43 (0.11, 0.75)	0.01
HIT-6, per 10 points	-5.61 (-7.81, -3.41)	<0.0001
Neck pain, present-absent	-5.46 (-9.35, -1.57)	0.006
Transient visual obscurations, present-absent	-7.62 (-11.91, -3.32)	0.001
Binocular diplopia, present-absent	-5.20 (-10.23, -0.17)	0.04

Abbreviations: CI = confidence interval; HIT-6 = 6-item Headache Impact Test; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire-25; PMD = perimetric mean deviation; VA = visual acuity.

vision-specific QOL measured by the NEI-VFQ-25 and Neuro-Ophthalmic Supplement were comparable to those for patients with MS (mean NEI-VFQ-25 composite score 87.7) and for patients with MS who had a history of acute optic neuritis (mean NEI-VFQ-25 composite score 82.4).^{9,18} Visual symptoms, headache, and sleep apnea risk, but not BMI, were associated with reduced QOL in our cohort.

This study expands on previous QOL studies showing reduced QOL in individuals with IIH shortly after diagnosis and in subjects with mild visual loss. It also expands on previous QOL studies^{3,4} that captured individuals within the first year of IIH diagnosis⁴ and those who had it chronically.³ Our study is unique in that it demonstrates QOL reduction before medical treatment, suggesting that the effects of intracranial hypertension, and not medication side effects, are the primary cause of symptoms resulting in poor QOL among patients with IIH.

Despite the mild visual loss in IIHTT participants, item scores on the Neuro-Ophthalmic Supplement were reduced in the areas of blurred vision, eyes feeling fatigued, and the patient feeling that the “2 eyes [were] seeing differently.” On the NEI-VFQ-25, the ocular pain and distance driving subscale scores were prominently affected. Transient visual obscurations, neck pain, and binocular diplopia were independently associated with a lower NEI-VFQ-25 composite score. While only 3% of patients had an esotropia and a sixth nerve palsy documented on examination, 18% complained of diplopia and eyes not working well together. These symptoms, along with headache, apparently are important correlates of visual QOL, and because they were associated with reduced SF-36 scores, they also seem to affect general QOL. The PMD in the best eye and the visual acuity in the worst eye also contribute to worsening of visual QOL. Because humans are foveate, patients are more aware of their central visual acuity, and many disorders affecting the peripheral vision do not become apparent until central acuity is affected. Then,

patients will promptly notice acuity in the worst eye, just as in other conditions that affect central visual acuity (e.g., optic neuritis, central serous retinopathy). However, patients will not notice visual field loss until the loss is more severe and bilateral; the visual field, therefore, in the best eye is more important than that in the worst eye. This may explain why the worst eye’s visual acuity, but the best eye’s PMD, is more important than the contralateral eye in each case.

Headache severity, as measured by the HIT-6, was associated with the NEI-VFQ-25 composite score, the Neuro-Ophthalmic Supplement score, and scores on SF-36. One might expect that headache alone would worsen QOL; however, others have reported that individuals with episodic migraine had QOL scores that were similar to those in the general population.¹⁹ This may be because most migraine headaches are intermittent and headache in IIH is usually chronic. Chronic migraine and chronic headaches associated with medication overuse are associated with worse QOL both directly and indirectly by worsening depression.²⁰ As is the case in patients with chronic migraine,^{21,22} headache seems to be a direct significant contributor to lower QOL in patients with IIH. In fact, the HIT-6 score was associated with every SF-36 subscale. Headache appears to affect even visual QOL. However, when we controlled for HIT-6 score in our multiple regression model (table 3), other factors besides pain accounted for decreases in QOL including visual acuity, PMD, diplopia, and transient visual obscurations. In addition, reviewing the univariate linear models for the NEI-VFQ-25 subscales (table e-1), both HIT-6 score and transient visual obscurations were most highly associated with QOL. In fact, the presence of transient visual obscurations was associated with nearly all aspects of visual QOL. Pain alone is not the sole determinant of reduced visual QOL in IIH.

Obesity is associated with lower QOL scores.^{23–27} Patients with IIH, however, compared with obese controls,³ showed lower scores on the SF-36. The obese controls in that study showed a higher incidence of depression and anxiety than individuals of normal weight. In this study, the presence of obesity was not associated with worse QOL in patients with IIH. Sleep apnea, however, may be an important obesity-related comorbidity leading to reduced QOL among patients with IIH as one would expect that nonrestorative sleep may worsen QOL. We investigated risk of sleep apnea in patients with IIH who did not have a history of sleep apnea. A high risk score on the Berlin Sleep Apnea Questionnaire was associated with lower scores on the NEI-VFQ-25, the SF-36 Physical and Mental Component Summaries, and the general health subscale on the SF-36 (tables 2

and e-1). Furthermore, several studies have shown reduced QOL among patients with obstructive sleep apnea.^{28,29} In addition, QOL in patients with sleep apnea is associated with their daytime sleepiness.³⁰ Fatigue is a common complaint in IIH.³ While we did not directly assess fatigue, we observed a reduced SF-36 vitality subscale score compared with national normative data, and a high-risk Berlin Sleep Apnea score correlated with worse SF-36 vitality score. Therapies that address sleep apnea, fatigue, or both may be helpful in reducing the morbidity associated with IIH.

Several series regarding patients with IIH have reported cognitive dysfunction associated with a lower NEI-VFQ-25 composite score and Neuro-Ophthalmic Supplement score.³¹ It may be that symptoms of cognitive dysfunction also contribute to a lower QOL.

A limitation of this study is the absence of weight-matched controls. However, our findings parallel other controlled QOL studies^{3,4} in which QOL scores in controls were similar to published national norms.^{9,10} We did not assess participants for depression or directly investigate fatigue. These may be important determinants of QOL in IIH. Another limitation is that individuals completed the questionnaires at various times after the lumbar puncture required for IIH diagnosis. The lumbar puncture could conceivably confound some of the QOL scales. However, since study participants completed questionnaires about 1 week after the lumbar puncture, it is less likely to be an important factor.

IIH markedly affects QOL. Visual loss, headache, neck pain, transient visual obscurations, and binocular diplopia are all independently associated with poorer QOL in IIH with mild visual loss. Vision-related QOL in IIH is similar to that measured in other chronic neurologic disorders such as MS. IIH appears to affect QOL even at the time of diagnosis, and aggressively reducing the increased intracranial pressure may improve QOL over time. Further studies and treatments should address factors most affecting QOL; such treatments may augment the beneficial effects of weight reduction and pharmacologic therapies. Reduced QOL is a major morbidity of IIH and appears largely related to symptoms of increased intracranial pressure. Acetazolamide may improve the QOL of patients with IIH and thus may be useful, even in patients who do not appear to be at risk of substantial visual loss.¹⁵

AUTHOR CONTRIBUTIONS

Kathleen B. Digre: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis, study supervision. Beau B. Bruce: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and

will give final approval, statistical analysis. Michael P. McDermott: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Kristin M. Galetta: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Laura J. Balcer: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis, obtaining funding. Michael Wall: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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REFERENCES

1. 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.
2. Wall M, George D. Idiopathic intracranial hypertension: a prospective study of 50 patients. *Brain* 1991;114:155–180.
3. Kleinschmidt JJ, Digre KB, Hanover R. Idiopathic intracranial hypertension: relationship to depression, anxiety, and quality of life. *Neurology* 2000;54:319–324.
4. Daniels AB, Liu GT, Volpe NJ, et al. Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). *Am J Ophthalmol* 2007;143:635–641.
5. Smith JL. Whence pseudotumor cerebri? *J Clin Neuroophthalmol* 1985;5:55–56.
6. Frisén L. Swelling of the optic nerve head: a staging scheme. *J Neurol Neurosurg Psychiatry* 1982;45:13–18.
7. Scott CJ, Kardon RH, Lee AG, Frisen L, Wall M. 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.
8. Mangione CM. The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25). Scoring Algorithm, August 2000 [online]. Available at: https://www.nei.nih.gov/sites/default/files/nei-pdfs/manual_cm2000.pdf. Accessed November 17, 2014.
9. Raphael BA, Galetta KM, Jacobs DA, et al. Validation and test characteristics of a 10-item neuro-ophthalmic supplement to the NEI-VFQ-25. *Am J Ophthalmol* 2006;142:1026–1035.
10. Ware JE Jr, Kosinski M. The SF-36 Physical and Mental Health Summary Scales: A Manual for Users of Version 1, 2nd ed. Lincoln, RI: QualityMetric, Inc.; 2001.
11. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003;12:963–974.

12. Zeileis A. Object-oriented computation of sandwich estimators. *J Stat Soft* 2006;16:1–16.
13. Mallows CL. Some comments on Cp. *Technometrics* 1973;15:661–675.
14. Mallick H, Yi N. Bayesian methods for high dimensional linear models. *J Biomet Biostat* 2013;1:005.
15. Wall M, McDermott MP, Kieburz KD, 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.
16. Wall M, Kupersmith MJ, Kieburz KD, et al. The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. *JAMA Neurol* 2014;71:693–701.
17. Friedman DI, McDermott MP, Kieburz K, et al. The idiopathic intracranial hypertension treatment trial: design considerations and methods. *J Neuroophthalmol* 2014;34:107–117.
18. Mowry EM, Loguidice MJ, Daniels AB, et al. Vision related quality of life in multiple sclerosis: correlation with new measures of low and high contrast letter acuity. *J Neurol Neurosurg Psychiatry* 2009;80:767–772.
19. Santanello NC, Hartmaier SL, Epstein RS, Silberstein SD. Validation of a new quality of life questionnaire for acute migraine headache. *Headache* 1995;35:330–337.
20. Kim SY, Park SP. The role of headache chronicity among predictors contributing to quality of life in patients with migraine: a hospital-based study. *J Headache Pain* 2014;15:68.
21. Stuginski-Barbosa J, Dach F, Bigal M, Speciali JG. Chronic pain and depression in the quality of life of women with migraine: a controlled study. *Headache* 2012;52:400–408.
22. Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6) across episodic and chronic migraine. *Cephalalgia* 2011;31:357–367.
23. Forhan M, Gill SV. Obesity, functional mobility and quality of life. *Best Pract Res Clin Endocrinol Metab* 2013;27:129–137.
24. Taylor VH, Forhan M, Vigod SN, McIntyre RS, Morrison KM. The impact of obesity on quality of life. *Best Pract Res Clin Endocrinol Metab* 2013;27:139–146.
25. Burkert NT, Freidl W, Muckenhuber J, Strongegger WJ, Rasky E. Self-perceived health, quality of life, and health-related behavior in obesity: is social status a mediator? *Wien Klin Wochenschr* 2012;124:271–275.
26. Bentley TG, Palta M, Paulsen AJ, et al. Race and gender associations between obesity and nine health-related quality-of-life measures. *Qual Life Res* 2011;20:665–674.
27. Cardin F, Ambrosio F, Amodio P, et al. Quality of life and depression in a cohort of female patients with chronic disease. *BMC Surg* 2012;12(suppl 1):S10.
28. Fornas C, Ballester E, Arteta E, et al. Measurement of general health status in obstructive sleep apnea hypopnea patients. *Sleep* 1995;18:876–879.
29. D'Ambrosio C, Bowman T, Mohsenin V. Quality of life in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure—a prospective study. *Chest* 1999;115:123–129.
30. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540–545.
31. Yri HM, Fagerlund B, Forchhammer HB, Jensen RH. Cognitive function in idiopathic intracranial hypertension: a prospective case-control study. *BMJ Open* 2014;4:e004376.

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