Visual Field Outcomes for the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT)

Michael Wall,1,2 Chris A. Johnson,2 Kimberly E. Cello,3 K. D. Zamba,4 Michael P. McDermott,5 and John L. Keltner3,6; for the NORDIC Idiopathic Intracranial Hypertension Study Group

PURPOSE. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) showed that acetazolamide provided a modest, significant improvement in mean deviation (MD). Here, we further analyze visual field changes over the 6-month study period.

METHODS. Of 165 subjects with mild visual loss in the IIHTT, 125 had perimetry at baseline and 6 months. We evaluated pointwise linear regression of visual sensitivity versus time to classify test locations in the worst MD (study) eye as improving or not; pointwise changes from baseline to month 6 in decibels; and clinical consensus of change from baseline to 6 months.

RESULTS. The average study eye had 36 of 52 test locations with improving sensitivity over 6 months using pointwise linear regression, but differences between the acetazolamide and placebo groups were not significant. Pointwise results mostly improved in both treatment groups with the magnitude of the mean change within groups greatest and statistically significant around the blind spot and the nasal area, especially in the acetazolamide group. The consensus classification of visual field change from baseline to 6 months in the study eye yielded percentages (acetazolamide, placebo) of 7.2% and 17.5% worse, 35.1% and 31.7% with no change, and 56.1% and 50.8% improved; group differences were not statistically significant.

CONCLUSIONS. In the IIHTT, compared to the placebo group, the acetazolamide group had a significant pointwise improvement in visual field function, particularly in the nasal and pericentral areas; the latter is likely due to reduction in blind spot size related to improvement in papilledema. (ClinicalTrials.gov number, NCT01003659.)

Keywords: idiopathic intracranial hypertension, pseudotumor cerebri, perimetry, visual field, clinical trial

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) is a multicenter randomized, double-blind, placebo-controlled study that evaluated the efficacy of a weight reduction and low-sodium diet plus acetazolamide versus the diet plus placebo in reducing or reversing visual field loss in subjects with mild visual loss. We found the acetazolamide group had significantly improved perimetric mean deviation (MD), papilledema grade, quality of life measures, and cerebrospinal fluid (CSF) pressure.1

It is well known that visual field defects in idiopathic intracranial hypertension (IIH) can be improved with treatment2 and can be due to a variety of mechanisms. The main mechanism is thought to be CSF pressure-related disruption of axonal transport3,4 leading to intraneuronal optic nerve ischemia at the level of the optic nerve head. Another common mechanism is enlargement of the blind spot; this type of visual loss, mostly from peripapillary hyperopia, is refractive in origin.5 Less common causes of visual loss are fluid tracking from the optic disc to the fovea (neurosensory detachment) and the refractive visual loss related to choroidal folds.6

A study of patients with highly asymmetric papilledema has suggested a model of visual loss in IIH characterized by a generalized depression of the visual field.7,8 The model predicts visual loss greater in magnitude with increasing visual field eccentricity. This and another study concluded that the amount of visual loss correlates with the severity of optic disc edema—eyes with more optic disc edema generally had more visual loss.7,8 This relationship between degree of papilledema and visual loss suggests that visual loss in IIH occurs due to papilledema and not from a retrolaminar mechanism.

Our main outcome measure for the IIHTT was the change in the average perimetric MD from baseline to 6 months. We chose this measure because of evidence that visual loss in IIH occurs across the visual field and increases with eccentricity. Here we report additional visual field outcomes at 6 months in the IIHTT.
Visual Field Outcomes

### Table 1. Classification of Visual Field Abnormalities in the IIHTT

<table>
<thead>
<tr>
<th>Enlarged Blind Spot (EBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized depression</td>
</tr>
<tr>
<td>Widespread (Wsp)</td>
</tr>
<tr>
<td>Arcuate nerve fiber bundle defects (NFB)</td>
</tr>
<tr>
<td>Nasal Step (NS)</td>
</tr>
<tr>
<td>Pericentral (Pc)</td>
</tr>
<tr>
<td>Partial arcuate (Parc)</td>
</tr>
<tr>
<td>Arcuate (Arc)</td>
</tr>
<tr>
<td>Other including neurologic-like</td>
</tr>
<tr>
<td>Vertical Step (VS)</td>
</tr>
<tr>
<td>Quadrant (Q)</td>
</tr>
<tr>
<td>Superior depression (SD)</td>
</tr>
<tr>
<td>Inferior depression (ID)</td>
</tr>
<tr>
<td>Partial peripheral rim (PPR)</td>
</tr>
<tr>
<td>Central</td>
</tr>
<tr>
<td>Paracentral (Pc)</td>
</tr>
<tr>
<td>Normal</td>
</tr>
</tbody>
</table>

**METHODS**

**Subject and Visual Field Examination Eligibility**

A total of 165 subjects aged between 18 and 60 years who met the modified Dandy criteria for IIH were randomized if they had bilateral optic disc swelling, elevated intracranial pressure, and reproducible mild visual field loss with an average perimetric MD of $-2$ to $-7$ dB in the study (worst) eye; other minor eligibility criteria can be found in other publications. A data and safety monitoring committee monitored the ethical conduct of the study and the accumulated data for evidence of adverse treatment effects. The research adhered to the tenets of the Declaration of Helsinki.

To meet visual field eligibility criteria, subjects completed two screening visual field examinations at least 30 minutes apart using the SITA Standard 24-2 test pattern on the Humphrey Field Analyzer (HFA) II perimeter (model 750), with at least one set of screening examinations performed after the lumbar puncture. Both eyes were tested and the eye with the most negative MD (greater visual field loss) was designated as the study eye. The two sets of visual fields were averaged to obtain the mean baseline MD for each of the study and nonstudy eyes. The examinations were required to have adequate gaze tracking, meet IIHTT reliability criteria of $< 15\%$ false positives and $< 33\%$ fixation losses, and demonstrate reproducible visual loss on both sets of examinations at baseline and 6 months. Follow-up examinations were obtained at 1, 2, 3, 4, 5, 6, 9, and 12 months and at yearly visits; only data from the first 6 months (double-blind treatment period) are reported here.

We used the MD on the HFA as a global measure of visual function and as the primary measure of outcome in the IIHTT. We chose MD because of its more stable retest variability compared to individual or groups of test locations and its sensitivity to global, clinically meaningful changes in IIH.

**Pointwise Linear Regression (PLR)**

Data from the HFA were converted using Peridata (PeriData.Net; PeriData Software GmbH, Hürth, Germany) and uploaded into a spreadsheet program (Excel; Microsoft Corp., Redmond, WA, USA). For each of the 121 subjects completing the 6-month visit and having baseline, and those completing the 6-month visit and having at least two other visual field examinations, a linear regression analysis was performed with the dB measurement as the outcome variable and time as the independent variable. Results of the two baseline and two final visits were averaged for this analysis. This was done for each subject and each of the 52 non-blind spot test locations. For each test location, the results were summarized as the percentage of subjects with a positive slope and the treatment groups were compared with respect to these percentages using chi-square tests. There were 7 subjects in the IIHTT that were deemed treatment failures. These subjects did not have a sufficient number of visual field examinations for PLR so they are not included in the PLR analysis.

**Initial Versus Final Pointwise Outcome in dB**

At each location of the visual field, we compared the mean change in dB from baseline to month 6 between the acetazolamide and placebo groups using two-sample $t$-tests. Values from the seven treatment failure patients are included (the results from the time of treatment failure are carried forward to the 6-month time point). The comparisons were also carried out at various eccentricity zones of the visual field (Supplementary Fig. S1) by taking the MD across the individual points within each zone. The zones were defined by their Euclidian distance from the optic nerve.

**Visual Field Abnormality Classification**

For classification, we have refined the methodology from previous UC Davis Visual Field Reading Center (VFRC) studies. The classification system of the IIHTT contained six categories (enlarged blind spot, generalized depression, arcuate nerve fiber bundle, neurologic-like/other, central and normal). The categories were subdivided into more specific classes as shown in Table 1. The visual field abnormalities from 125 subjects who completed visual field examinations at both baseline and 6 months were classified into these six categories and specific classes as well as judged by three VFRC readers to be either improved, worse, or the same at the 6-month visit relative to baseline (reasons for failure to complete the 6-month double-blind treatment phase are found in the primary IIHTT article). The distribution of the consensus rating of visual field change was compared between the acetazolamide and placebo groups using a $\chi^2$ test. The analyses were repeated including the seven subjects who met criteria for treatment failure prior to month 6, with the visual field change classified as "worse." An abnormal perimetry exam in the IIHTT was defined as meeting any of the following criteria (with the exception of an enlarged blind spot): (1) a glaucoma hemifield test (GHT) outside of normal limits; (2) pattern standard deviation value (PSD) $P < 5\%$; (3) a single point worse than the 0.5% pointwise probability level on the total and/or pattern deviation probability plots; (4) two clustered points beyond normal limits ($P < 5\%$) in a clinically suspicious area, and at least one point worse than the 1% level on the total and/or pattern deviation Plot (a cluster is defined as two or more horizontally or vertically—not diagonally—contiguous abnormal points with $P < 5\%$); (5) two or more points beyond normal limits ($P < 5\%$) in and/or around the peripapillary zone; (6) three or more clustered points worse than the 5% level on the total and/or pattern deviation plot and a pattern of loss consistent with ocular pathology. The predominant pattern of loss was used to determine the abnormality classification defined in Table 1. For a hemifield to be classified as normal, it had to meet any of the above criteria for hemifield abnormality.
Classification Procedures

The procedures for hemifield classification were as follows: The superior and inferior hemifields of visual field examinations for the two examinations at baseline and the two examinations at 6 months were evaluated separately and, in general, the pattern on the deviation plot ("total" or "pattern") showing the greater number of abnormal points was used to determine the appropriate classification for a hemifield abnormality. However, the other deviation plot, as well as the gray scale, was evaluated to confirm the appropriateness of the classification. Abnormal test locations that were extraneous to the salient pattern were considered less important for the determination of the hemifield classification. Thus, the most predominant pattern was classified. Baseline and month 6 visual field examinations were evaluated in this report, which included 1511 of 1982 hemifields that met the IUIHTT criteria for abnormality. Since the readers were masked to the subject’s optic disc characteristics and randomized treatment assignment, the classification of the visual field deficit is strictly based on the pattern of abnormality.

Three readers (CAJ, KEC, JLK) reviewed 500 visual field examinations (1000 hemifields) at baseline and 491 (982 hemifields) at 6 months from 125 subjects who performed the two exams at baseline and the two exams at 6 months and classified the superior and inferior hemifields separately as to the presence of an abnormality that met the secondary criteria (Supplementary Table S1). Four subjects did not perform their second set of 6-month visual field examinations and one subject did not perform the right eye examination at month 6, thus a total of 9 examinations (18 hemifields) were not included in the analyses.

FIGURE 1. Mean threshold change in dB from baseline to 6 months at each test location within each treatment group, with positive values indicating improvement with the treatment failure subjects included. Note that the greatest changes occurred in the periphery and around the blind spot but improvement occurred across the visual field. Green: 2 dB or more improvement. Yellow: 1–2 dB improvement. Red: less than 1 dB improvement.

FIGURE 2. (A) Magnitude of treatment effect (acetazolamide–placebo) at each test location. (B) Value for statistical significance of the treatment effect at each test location; *P < 0.05* shown in darker green.
Reader Agreement

Agreement among the readers was summarized at both baseline and month 6 according to the percentage of hemifields for which none, two, or all three readers agreed on the 13 specific hemifield classifications. If at least two readers agreed with a hemifield classification, the majority classification was accepted (2 out of 3 readers in agreement). If all three readers disagreed, then the visual fields were adjudicated by group consensus to reach a final classification of the hemifield.

A logistic regression model was used to examine factors associated with the presence of a normal hemifield using the first examination at each time point. The model included terms for time (baseline, month 6), hemifield (superior, inferior), and eye (study eye, nonstudy eye); model parameters and standard errors were estimated using generalized estimating equations to account for the dependence among the eight observations for each person (2 time points × 2 hemifields × 2 eyes). These analyses used the results of the first of the two perimetry examinations at each time point.

RESULTS

Visual sensitivity improved across the visual field in the acetazolamide group over the 6-month intervention period with the magnitude of the change in dB greatest around the blind spot and the nasal area; with the treatment failure subjects included some test locations in the placebo worsened (Fig. 1, right). Figure 1 shows the mean changes from baseline to month 6 in dB for each treatment group; the group differences in mean change (acetazolamide values minus placebo values) are depicted in Figure 2A with corresponding pointwise P values in Figure 2B. There was an increase in treatment effect with eccentricity zone but this change did not reach statistical significance (Fig. 3).

The pointwise linear regression analyses showed that, on average, 36 of 52 visual field test locations had improving thresholds (positive slopes) in the study eye. While the PLR slopes improved in the majority of subjects at all locations in both treatment groups (Fig. 4), there were no significant differences between the treatment groups in the percentage of subjects with a positive slope.

The consensus rating results of visual field change from baseline to 6 months in the study eye are found in Table 2. When including subjects who met criteria for treatment failure, the percentages (acetazolamide and placebo) were 7.2% and 17.5% worse, 35.1% and 31.7% with no change, and 56.1% and 50.8% improved. The group differences were not statistically significant.

The hemifield abnormality classification frequencies are presented by hemifield and treatment assignment for the study and nonstudy eyes at baseline and 6 months in Supplementary Tables S2 through S4. Note the common occurrence of nerve fiber bundle defects. Also, normal hemifields were more common at month 6 (35.8%) than at baseline (11.8%; odds ratio [OR] 4.46, 95% confidence interval [CI] 2.99–6.64, P < 0.0001), more common in the superior hemifield (29.6%) than in the inferior hemifield (18%; OR 2.10, 95% CI 1.57–2.82, P < 0.0001), and less common in the study eye (16.8%) than in the fellow eye (30.8%; OR 0.43, 95% CI 0.32–0.57, P < 0.0001).

Shown in Table 3 are the distributions of the change in MD corresponding to the consensus rating of visual field change in the study eye (treatment failure subjects not included). On
average there was an approximately 2-dB MD change in the subjects classified as changing in either direction. Readers showed high levels of agreement with respect to hemifield abnormality classification, with the percentages of hemifields on which 2/3 or 3/3 readers agreed on the classification ranging from 84% to 95% (Supplementary Table S5).

**DISCUSSION**

In this more detailed analysis of the visual field data from IIHTT participants, we found pointwise improvement across the visual field in both treatment groups except for the areas of loss in the placebo group (in dB) when the treatment failure subjects were included. In terms of changes in visual sensitivity in dB, improvement was greater with eccentricity, especially nasally in the visual field and adjacent to the blind spot. Analysis of PLR, which did not include the treatment failure subjects (due to an insufficient number of data time points), showed improvement in both treatment groups on average over the 6-month time period in over two-thirds of test locations. The consensus ratings of the three readers also showed that most subjects improved or stayed the same.

In a previous study, it was shown that IIH patients with highly asymmetric papilledema generally have more loss in the eye having the higher papilledema grade. The visual field function of the eye with the lower grade is also abnormal across the visual field when compared to controls. The visual damage in this prior study in both the higher and lower grade eyes included fixation and the magnitude of the loss increased with eccentricity. We have proposed a model of visual loss in IIH based on these findings characterized by a generalized depression of the visual field with increasing loss with eccentricity (Fig. 5). While nerve fiber bundle-like defects are frequently observed (especially inferior nasal nerve fiber bundle defects), the overall pattern when multiple subjects are averaged is a generalized depression. The results of the IIHTT support this model of visual loss in IIH. Studies have also shown that the amount of visual loss is associated with the severity of papilledema. This relationship suggests that visual loss in IIH occurs due to papilledema and not to a retrolaminar mechanism.

In conclusion, both the acetazolamide and placebo groups showed there was significantly more visual field improvement in the acetazolamide group than in the placebo group, no significant differences were found with PLR or consensus of clinical readers. Again, this lack of difference likely relates to both groups improving, the lack of a substantial amount of visual loss at baseline and the categorical nature of some of the measures.

The magnitudes of the pointwise changes found were modest. This likely related to our entry criteria that required a MD between −2 and −7 dB to be enrolled. Most of the MDs were closer to the −2 dB end of the distribution as the mean MD in each treatment group at study onset was −3.5 dB. Therefore, there was likely a floor effect and little room for many subjects to improve. Although pointwise dB analysis showed there was significantly more visual field improvement in the acetazolamide group than in the placebo group, no significant differences were found with PLR or consensus of clinical readers. Again, this lack of difference likely relates to both groups improving, the lack of a substantial amount of visual loss at baseline and the categorical nature of some of the measures.

In conclusion, both the acetazolamide and placebo groups in the IIHTT demonstrated improvement across the visual field increasing with eccentricity, especially nasally; there was also substantial improvement in the visual field around the blind spot. This supports use of the MD as a useful measure to follow IIH patients over time.

**Acknowledgments**

Supported by NEI Grant NORDIC 1U10EY017281-01A1. The authors alone are responsible for the content and writing of the paper.
References


Appendix

Nordic Idiopathic Intracranial Hypertension Study Group

Ccoinvestigator CCoinvestigators/Sites: New York Eye and Ear Infirmary: Rudrani Banik, MD (principal investigator), Sanjay Kedhar, MD (sub-investigator), Flora Levin, MD (investigator), Jonathan Feistmann, MD (investigator), Katy Tai, MA (co-investigator), Alex Yang, BA (co-coordinator), Karen Tobias, BA (coordinator), Melissa Rivas, BA (co-coordinator), Lorena Dominguez, BA (coordinator), Violete Perez, BA (coordinator); University of Iowa and Department of Veterans Affairs: Reid Longmuir, MD (principal investigator), Matthew Thurtell, MBBS, MSc (sub-investigator), Trina Eden (coordinator), Randy Kardon, MD, PhD (sub-investigator); The Eye Care Group: Robert Lesser, MD (principal investigator), Yanina O'Neil, MD (sub-investigator), Sue Heaton, BS, CCRC (co-coordinator), Nathalie Gintowt (co-coordinator) Danielle Rudich (co-coordinator), University of Utah: Kathleen Digre, MD (principal investigator), Judith Warner, MD (sub-investigator), Barbara Hart, BS (co-coordinator), Kimberly Wegner, BS (co-coordinator), Bonnie Carlstrom, COA (coordinator), Susan Allman (co-investigator), Bradley Katz, MD, PhD (sub-investigator), Anne Haroldsen (regulatory); Bascom Palmer Eye Institute, University of Miami: Byron L. Lam, MD (principal investigator), Joshua Pasol, MD (sub-investigator), Potyra R. Rosa, MD (co-investigator), Alexis Morante, MS (co-coordinator), Jennifer Verriotto, MS (co-coordinator); Bethesda Neurology, LLC: David Katz, MD (principal investigator), Tracy Ashbury (coordinator), Robert Gerwin, MD (sub-investigator), Mary Barnett (data entry); Swedish Medical Center: Steven Hamilton, MD (principal investigator), Caryl Tengco (coordinator), Beena Gangadharan (co-coordinator), Eugene May, MD (sub-investigator); Dean A. McGee Eye Institute: Anil Patel, MD (principal investigator), Bradley Farriss, MD (sub-investigator), R. Michael Siatkowski, MD (sub-investigator), Heather Miller, LPN (coordinator), Vanessa Bergman (co-coordinator), Kammerin White (co-investigator), Steven O’Dell (lumbar puncture), Joseph Andrezik (lumbar puncture), Timothy Tytle (lumbar puncture); University of Pennsylvania: Kenneth Shindler, MD, PhD (principal investigator), Joan Dupont (co-investigator), Rebecca Salvo (co-coordinator), Sheri Drossner (co-coordinator), Susan Ward (co-investigator), Jonathan Lo (co-coordinator), Stephanie Engelhard (co-investigator), Elizabeth Windsor (coordinator), Sami Khella (lumbar puncture), Madhura Tamhankar, MD (sub-investigator); Washington University in St. Louis School of Medicine: Gregory Van Stavern, MD (principal investigator), Jamie Kambarian (co-investigator), Renee Van Stavern, MD (sub-investigator), Karen Civitelli (Regulatory), J. Banks Shepherd, MD (sub-investigator); Emory University: Beau B. Bruce, MD (principal investigator), MS; Valérie Biousse (co-investigator), Sue Heaton, BS, CCRC (co-coordinator), Robert Lesser, MD (principal investigator), Yanina O’Neil, MD (sub-investigator), Karen Searcey (co-coordinator), Lanning Kline, MD (sub-investigator), Roy McDonald (coordinator); Raleigh Neurology Associates, PA: Syndee J. Givre, MD, PhD (principal investigator), Tippi Hales (co-coordinator), Penni Bye (co-coordinator), Kelly Fuller (co-coordinator), Kenneth M. Carnes, MD, (sub-investigator), Kimberly James (Regulatory), Jennifer Verriotto, MS (co-coordinator); University of Alabama Birmingham: Michael Vaphiades, DO (principal investigator), Karen Searcey (co-coordinator), Lanning Kline, MD (sub-investigator), Roy McDonald (coordinator); New York Eye & Ear Infirmary: Rudrani Banik, MD (principal investigator), Tippi Hales (co-coordinator), Penni Bye (co-coordinator), Kelly Fuller (co-coordinator), Kenneth M. Carnes, MD, (sub-investigator), Kimberly James (Regulatory), Mary Barnett (lumbar puncture)
Consultant: Richard Mills, MD (Glaucoma Consultants Northwest)

Data Safety Monitoring Board Members: Maureen Maguire, PhD (Chair; University of Pennsylvania); William Hart Jr, MD, PhD; Joanne Katz, ScD, MS (Johns Hopkins); David Kaufman, DO (Michigan State University); Cynthia McCarthy, DHCE MA; John Selhorst, MD (Saint Louis University School of Medicine)

Adjudication Committee: Kathleen Digre, MD (University of Utah); James Corbett, MD, FAAN (University of Mississippi Medical Center); Neil R. Miller, MD (Johns Hopkins University); Richard Mills, MD (Glaucoma Consultants Northwest)