Factors Affecting Visual Field Outcomes in the Idiopathic Intracranial Hypertension Treatment Trial

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Background: To determine the prevalence of visual field (VF) performance failures (PF) and treatment failures (TFs), and identify factors associated with PFs in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).

Methods: A total of 165 participants from 38 sites with idiopathic intracranial hypertension (IIH) and mild visual loss were randomized to either acetazolamide-plus diet or placebo-plus diet. The IIHTT Visual Field Reading Center evaluated 2950 Swedish Interactive Threshold Algorithm Standard 24-2 VFs from the enrolled participants. A TF was defined when the participant's VF mean deviation (MD) worsened $\geq$2 to 3 dB from the average baseline MD (range of -2 to -7 dB) with a second retest confirming the visual deterioration. A PF was determined when the participant's: 1) VF results met TF criteria but were not confirmed on retest, 2) deterioration was confirmed on retest but the IIHTT Adjudication Committee concluded a TF was clinically unlikely.

Results: TF was detected in 7/165 (4%) of the participants and PF was detected in 35/165 (21%) of the participants on at least 1 examination. Four of the 35 PFs were adjudicated for TF, however based on clinical review by the adjudication committee and a third retest, they were judged as PFs. Of the 2,950 total IIHTT VF examinations, 2.7% met PF criteria.

Conclusions: PF was confirmed in 21% of subjects and in 2.7% of the total number of VF examinations and was reversible on repeat testing. We recommend retesting when perimetric worsening occurs in otherwise clinically stable or improving IIH patients.

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Idiopathic intracranial hypertension (IIH) is a disorder of elevated intracranial pressure (ICP) of unknown cause that mainly occurs in overweight women (1,2). The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) was a multicenter, randomized, double-blind, placebo-controlled trial seeking to evaluate the efficacy of weight reduction and low sodium diet plus acetazolamide vs the same diet plus placebo in reducing visual field loss. The study demonstrated that participants in the acetazolamide-plus-diet group had significantly improved visual field function, papilledema grade, quality of life measures, and ICP relative to the placebo-plus-diet group (3).

Since perimetry is a psychophysical measure, the thresholds obtained are not dependent on the functional architecture of the visual system alone but also on a variety of physical and behavioral factors. For example, improper refraction (4), lens rim artifact (5), pupillary constriction (6) or dilation (7), and blepharoptosis (8) all affect luminance detection thresholds. In addition, behavioral factors including subject attention (9), alertness, motivation, fatigue, improper instructions, and related response bias (10) can influence thresholds. It also has been shown that reading standardized instructions to the participant before testing is effective in reducing variability (10).

During the course of the IIHTT, we found some participants with substantial worsening of their mean

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deviation (MD). Some of these participants had related worsening of other clinical symptoms and MD deterioration was confirmed on a repeat perimetric examination. These subjects, termed treatment failures (TFs), are the subject of a separate report (11). Additional participants who also had a marked deterioration in their MD were otherwise stable on repeat examination. We categorized these latter participants as performance failures (PFs), who had difficulty in performing the perimetric test. In this report, we examined the findings of the IIHTT participants with TF and PF and analyzed the associated factors of these 2 groups.

METHODS

The IIHTT enrolled 165 participants who met the modified Dandy criteria for IIH from 38 Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) network sites (12–15). Written informed consent was obtained from the participants, the study was compliant under the Health Insurance Portability and Accountability Act and followed the tenets of the Declaration of Helsinki, and the research was approved by the Institutional Review Board at each clinical site. A Data Safety and Monitoring Committee examined the ethical conduct of the study and the acquisition of data for evidence of adverse and beneficial treatment effects.

Participants with IIH between the ages of 18 and 60 years were enrolled in the study if they had the presence of bilateral optic disc swelling, elevated ICP, and reproducible mild visual field loss with an average perimetric MD of −2 dB to −7 dB in the affected eye (worse eye); other minor inclusion and exclusion criteria can be found elsewhere (12). Participants were then randomized into one of 2 treatment groups; diet + acetazolamide or diet + placebo and were followed for 6 months at which time the primary and secondary outcomes were investigated (12).

Perimetry was performed by a certified visual field technician at the participant's screening, baseline, and 1, 2, 3, 4.5, 6, 9, 12 month and subsequent yearly visits. The Visual Field Reading Center (VFRC) contacted each certified clinical technician who was instructed to; 1) provide proper participant ergonomics, 2) provide frequent breaks (especially between testing each eye), 3) properly align the trial lens to the eye, 4) confirm the participant was well rested, 5) make sure the participant was alert, 6) give clear, standardized testing instructions, 7) maintain eye monitoring throughout the exam, and 8) remain with the participant during testing.

During the screening visit, participants underwent at least 2 visual field examinations at least 30 minutes apart using the Swedish Interactive Threshold Algorithm (SITA) Standard 24-2 test pattern on the Humphrey Field Analyzer II perimeter (Model 750), with at least 1 set of screening visual fields performed after the lumbar puncture (14,15). Both eyes were tested and the eye with the most negative MD (greater visual field loss) was designated as the study eye (affected eye). The 2 sets of visual fields from the study and nonstudy eyes were averaged for the mean baseline MD.

To meet study visual field eligibility criteria, all perimetry examinations were required to have: 1) adequate gaze tracking (fixation monitoring) (16), 2) meet reliability standards of fixation loss errors <33% and false-positive errors <15%, 3) demonstrate reproducible visual loss on both sets of fields (at baseline and 6 months), and 4) exhibit an average MD between −2 and −7 dB at the baseline perimetric examinations. With increasing visual field damage in stable glaucoma patients, Bengtsson et al reported large degrees of intertest variability with false-negative (FN) errors (17,18). After approximately 10 dB of loss, these errors are most commonly related to visual field damage rather than to poor performance. For that reason, we did not use FNs as an indicator of visual field reliability.

Visual field examinations that were unreliable and/or differed in MD by >4 dB were repeated. If the abnormalities in the 2 sets of baseline or 6-month examinations were not reproducible, a retest was also required.

In the IIHTT, a TF was defined when a participant with an average baseline MD of −2 dB to ≤−3.5 dB worsened by more than 2 dB MD from the average baseline values in either eye, or when a participant with an average baseline MD between −3.5 dB and −7 dB had visual function worsen by more than 3 dB MD from baseline in either eye (11). Wall et al (19) demonstrated that on retesting glaucoma patients with a range of MD, variability increased in increasing visual field damage. We used this piece of data to approximate the 95% confidence bounds and cutoffs for TF.

For confirmation of these cases, a perimetric retest was performed after at least 1 hour but within 4 days of the

TABLE 1. Visual field examinations meeting treatment failure criteria in performance and treatment failure subjects

Group	Subjects (n = 165)	% of Subjects	VFs (n = 2950)	% of VFs
Performance failure	35	21	79	2.7
Treatment failure	7	4	54	1.8
Total	42	25	133	4.5

VF, visual field.

TABLE 2. Visual field examinations meeting treatment failure criteria in study/nonstudy eyes of performance and treatment failure subjects

	Number of Visual Field Examinations					
Group	Criteria Met in Both Eyes	%	Criteria Met in Study Eye Only	%	Criteria Met in Nonstudy Eye Only	%
Performance failure (n = 79 VFs)	49	62	4	5	26	33
Treatment failure (n = 54 VFs)	48	89	6	11	0	0

VF, visual field.

original visual field examination. The clinical site was also informed that the participant should be well rested, alert, and feeling well when the retest was performed. A possible IIHTT visual field PF was defined as a perimetry result that met the criteria for TF but returned to acceptable MD limits of variability after retest. On 4 occasions, a third retest was required to distinguish between a PF and a TF. If a TF was confirmed, the participant's visual field examinations and all clinical information such as visual acuity, Amsler grid, color plate test results, presence of a relative afferent pupillary defect, and changes in optic disc swelling were reviewed by the IIHTT Adjudication Committee. The committee would then decide whether the TF was most likely due to worsening of IIH or whether there was another more likely cause (such as presence of another disease process or a PF) (13). Participants who were classified as TFs were referred to their physicians for further treatment decisions rather than staying on study treatment protocol and were followed at the usual study intervals.

RESULTS

Of the 2,950 visual field examinations performed by the 165 IIHTT participants throughout the study, Table 1 shows 42 (25%) participants had 133 visual field examinations that met criteria for possible TF. Each of these 42 subjects had at least 1 examination that met the perimetric TF criteria. Seven of these participants (4% of 165 total participants) were classified as TFs as the worsening of the MD was confirmed on retest, whereas 35 (21%) were classified as PFs as the worsening was not confirmed on retest.

The 35 PFs had 79 visual field examinations (2.7% of the total of all visual field examinations) that met perimetric TF criteria. However, on retest, most of the visual field results did not confirm the initial worsening of the MD and were reversible on repeat testing. Thus, these subjects were deemed as PFs. In most of the cases (62%), results from both eyes from the same participant met perimetric TF criteria rather than 1 single eye from the same participant (Table 2).

As shown in Table 3, most (74%) of the examinations from 30 of the 35 participants originally met criteria for possible TF but returned to acceptable MD limits on the next retest. A total of 23% of the examinations from 4 participants did not return to acceptable MD limits on retest. All of their available clinical participant information was submitted to the adjudication committee for TF review, which concluded that these participants were PFs rather than TFs and suggested further follow-up retests. These subjects had either improving or stable clinical features and all had difficulty performing the perimetric examination according to the site.

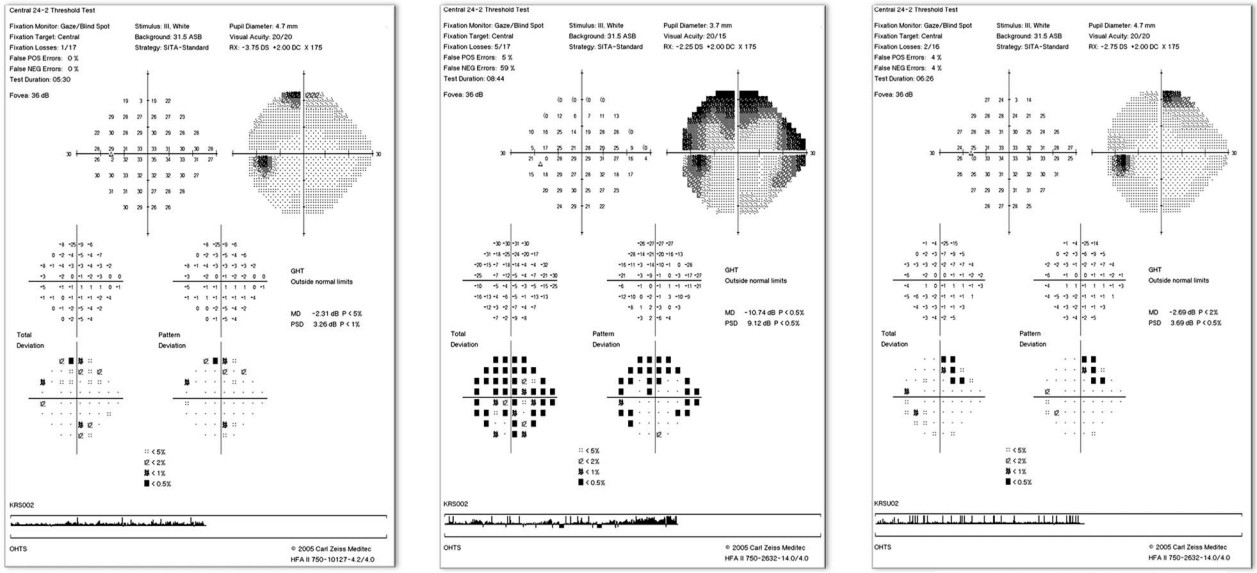
Visual field result examples demonstrating improvement on the next retest are shown in Figures 1 and 2. Each of the figures demonstrates visual field examinations where a follow-up test met TF criteria and the next examination returned to acceptable MD limits. Figure 1 is the most extreme PF example with an 8.43 dB MD shift of worsening from the screening visit to the follow-up examination and an 8.05 dB MD shift of improvement to the next follow-up examination. Figure 2 is a similar example but shows a case with "reliability criteria" that are in the acceptable range.

Seven of the 165 IIHTT participants were determined to be TFs by the IIHTT Adjudication Committee (11). On retest, these participants' visual field results confirmed the

TABLE 3. Performance failure visual field examinations meeting treatment failure criteria

Performance Failure (PF) Group	Number	%	Status
VFs meeting TF criteria which returned to acceptable MD limits on retest (30 subjects)	59	74	Considered performance failures
VFs meeting TF criteria which did not return to acceptable MD limits on retest (4 subjects)	18	23	Confirmed performance failures
VFs meeting TF criteria with no retest (1 subject)	2	3	Considered performance failure

MD, mean deviation; TF, treatment failure; VF, visual field.



Month 1 Visit (001)
MD: -2.31 dB

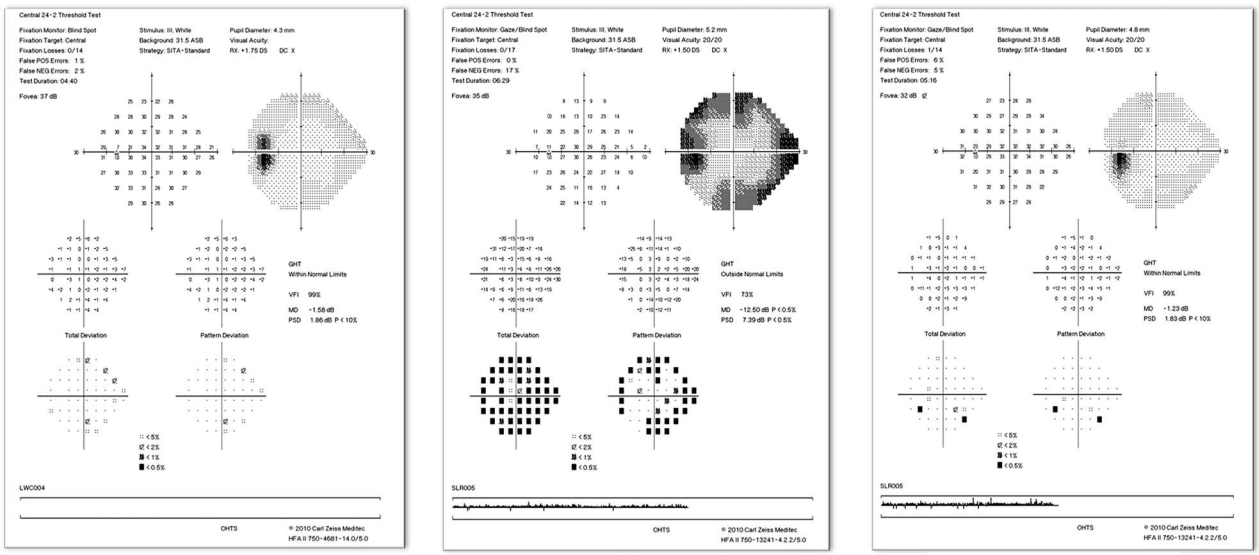
Month 2 Visit (002)
MD: -10.74 dB
Meets Treatment Failure Criteria

Unscheduled Visit (U01):
2 Weeks after Month 2 Visit
MD: -2.69 dB
No Longer Meets Treatment Failure Criteria

FIG. 1. Visual field performance failure example with a >8 dB MD shift. Follow-up visual field meets treatment failure criteria but returns to acceptable limits on retest. MD, mean deviation.

initial worsening of the MD and the committee decided elevated ICP was the most likely reason for the worsening of IIH. Six of the 7 (86%) participants were in the placebo group and 1 (14%) of the participants was in the acetazolamide group ($P = 0.06$) (12). In most of the cases (89%), results from both eyes from the same participant met TF criteria rather than 1 single eye from the same participant (Table 2).

As shown in Table 4, there was a low rate of cases categorized as unreliable based on fixation losses and



Month 4.5 Visit (004)
MD: -1.58 dB

Month 6 Visit (005)
MD: -12.50 dB
Meets Treatment Failure Criteria

Unscheduled Visit (U01):
1 Week after Month 6 Visit
MD: -1.23 dB
No Longer Meets Treatment Failure Criteria

FIG. 2. Visual field performance failure example with a >12 dB MD shift. Follow-up visual field meets treatment failure criteria but returns to acceptable limits on retest. MD, mean deviation.

TABLE 4. Perimetric "unreliability" in performance and treatment failure subjects

Group	Number of Visual Field Examinations											
	FN Errors	%	FL Errors	%	FP Errors	%	FL and FP Errors	%	Blind Spot Turned Off	%	Total	%
Performance failures												
VFs meeting PF criteria (n = 79)	20	25	7	9	3	4	0	0	0	0	30	38
Treatment failures												
VFs meeting TF criteria (n = 54)	15	28	2	4	0	0	0	0	0	0	17	32

FN, false negative; FL, fixed loss; FP, false positive; PF, performance failure; TF, treatment failure; VF, visual field.

TABLE 5. Perimetry false-negative responses in performance and treatment failure subjects

Group	Number of Visual Field Examinations	
	FN Errors	%
Performance failure (n = 745 VFs)	35	4.7
Treatment failure (n = 133 VFs)	21	15.8
Total	56	20.5

FN, false negative; VF, visual field.

false-positive responses with these measures occurring slightly more often in the PF group than the TF group. In Table 5, we report the results containing excessive FN errors ≥15% with more errors occurring in the TF group than the PF group.

DISCUSSION

To our knowledge, this is the first series of perimetry clinical trial patients with transient substantial worsening of the perimetric MD, apparently due to behavioral factors rather than disease worsening. PFs were an important confounding finding when adjudicating which subjects had worsening of their MD because of worsening of IIH (TFs). Since the examinations returned to baseline levels on retest, this confirms that there were perimetry performance issues rather than worsening of IIH. Our results show marked worsening of MD was much more likely to be due to PF than to worsening of IIH.

Perimetric worsening in the IIHTT occurred in 5 times as many subjects as visual field worsening related to IIH worsening. Because the IIHTT's VFRC quality control system provided regular performance feedback to the clinical center's technicians, it is unlikely that these factors were contributing to unreliable results (15). Only 1.4% of the 878 examinations performed by the PF and TF groups met the IIHTT unreliability criterion of ≥33% fixation losses or ≥15% false-positive errors. In the Ocular Hypertension Treatment Study (OHTS), ongoing and intensive monitoring with rapid feedback to technicians also reduced the frequency of unreliable examinations (20) and reading standard testing instructions to the participant before testing was effective in improving reproducibility (10).

False-positive catch trials are responses that occur independent of a perimetric stimulus. As perimetric software evolved to shorten testing times, blank presentations were replaced by tabulation of responses (21) that occur in an improbable response window such as before the minimal response time of a trial (180 milliseconds) or delayed responses to a trial (22). Here, an acceptance response time window is calculated for the subjects' true responses preceded by a "listen time" for responses occurring too soon to be physiologic ones or too late to be likely

related to the stimulus (22). These nonphysiologic, unexpected responses are defined as false-positive responses. Although the manufacturer flags false-positive rates above 33%, the 95% confidence interval in consecutive series of glaucoma patients using SITA is approximately 10% (23,24). Keltner et al experience with the Optic Neuritis Treatment Trial, and OHTS (25,26) showed that the false-positive rate (and rates of FN and fixation losses) could be substantially improved by training the perimetrist with periodic feedback. This response time window method estimates a different response reliability criterion compared with blank presentations as the 2 methods do not correlate well and the blank presentation method yields more frequent false positives, (24,27) likely because of observation that false positives are dispersed cross a trial (28).

The FN catch trial rate in normal participants is 1%–2% with well-trained perimetrists (29) and increases with decreasing visual sensitivity; (17,24) that is, most likely the reason for our high FN rates in TF subjects.

Fixation losses are even less reliable as they are often identified as abnormal when related to head tilts that occur during the examination (30). Use of the gaze tracker is beneficial for fixation monitoring and also gives information on eye closure, blinks, and ocular surface (tear film) abnormalities.

Another important finding of the study is that 87% of the perimetry results leading to a designation of PF had "reliability" criteria considered within normal limits. FN catch trials can identify subjects that perform well at the beginning of the test; however, attention to the test deteriorates as the test proceeds (Fig. 1). In addition, FNs may increase with visual field damage (24) and may not determine poor performance from criterion shifts or attention lapses throughout the test.

Many factors could have contributed to PF in the IIHTT: 1) falling asleep or becoming drowsy during testing, 2) blepharoptosis related to drowsiness, 3) influence of headache pain, 4) poor fixation monitoring/gaze tracking due to fatigue or poor ergonomics (9), 5) participant unattended during testing, 6) misaligned trial lens rim, and 7) inadequate or nonstandardized testing instructions leading to a change in response bias (10). When PF is suspected, we recommend having the patient return for a dedicated perimetry session when they are alert, well rested, properly aligned, and closely monitored by the technician throughout the perimetry examination. We believe that PFs can occur with any perimetric subject who is distracted or fatigued. The occurrence of this phenomenon in IIH may be more frequent than in other optic neuropathies including glaucoma because of the frequent presence of severe headache during the perimetric examination.

In the IIHTT, reversible substantial worsening of MD occurred in 2.7% of all visual field examinations and at least once in 21% of subjects. These subjects usually were not identified by test "reliability criteria" but rather by judgment of their performance by the perimetrist and their full clinical presentation. Since a worse MD was much more likely to be due to PF than to worsening of IIH, we recommend retesting these patients at a separate sitting when they are alert, well rested, and relatively free of headache.

STATEMENT OF AUTHORSHIP

Category 1: a. Conception and design: K. E. Cello; b. Acquisition of data: K. E. Cello, M. Wall; c. Analysis and interpretation of data: K. E. Cello, M. Wall, C. A. Johnson, J. L. Keltner. Category 2: a. Drafting the manuscript: K. E. Cello; b. Revising it for intellectual content: K. E. Cello, M. Wall, C. A. Johnson, J. L. Keltner. Category 3: a. Final approval of the completed manuscript: K. E. Cello, M. Wall, C. A. Johnson, J. L. Keltner. The NORDIC Idiopathic Intracranial Hypertension Study Group.

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