The IIHTT: a Multicenter, Double-Blind, Randomized Clinical Trial Comparing Acetazolamide and Placebo on Visual Outcome

On Behalf of the NORDIC IIH Study Group

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Case Presentation

- 37-year-old obese woman with 2 weeks of constant bi-occipital headaches
- 2 days of greying out centrally and fullness of ears (like hearing seagulls)
- 220 pounds currently with 50 pound gain over last 6 years
# Neuro-ophthalmic Exam

<table>
<thead>
<tr>
<th>Item</th>
<th>Result 1</th>
<th>Result 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acuity</td>
<td>20/30</td>
<td>20/40</td>
</tr>
<tr>
<td>Color</td>
<td>10/10</td>
<td>10/10</td>
</tr>
<tr>
<td>Pupils</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Motility</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Fundus</td>
<td>Grade 3</td>
<td>Grade 3</td>
</tr>
</tbody>
</table>
Humphrey 24-2 Fields

Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 0/18
False POS Errors: 0%
Test Duration: 06:38
Fovea: 34 dB

Date: 11-22-2011
Time: 3:05 PM
Age: 37

GHT
Outside normal limits
VFI 91%
MD -4.03 dB P 1.1%
PSD 3.62 dB P 0.9%

Total Deviation
Pattern Deviation

Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 1/18
False POS Errors: 2%
False NEG Errors: 15%
Test Duration: 06:56
Fovea: 36 dB

Date: 11-22-2011
Time: 3:55 PM
Age: 37

GHT
Outside normal limits
VFI 81%
MD -7.03 dB P 0.5%
PSD 8.64 dB P 0.5%

Total Deviation
Pattern Deviation
OCT scan
Diagnostic Testing and Therapy

- MRI and MRV of head were normal
- CSF normal profile with OP = 57 CM
- Started and maintained on 500 mg Diamox Sequel bid with regular follow up visits
- Resolution of headaches, TVO, pulsatile tinnitus
6 month FUV HVF

Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 1/11
False POS Errors: 6.5%
False NEG Errors: 0.5%
Test Duration: 03:00

Stimulus: III, White
Background: 31.5 ASB
Strategy: SITA-Fast

Pupil Diameter: 5.2 mm
Visual Acuity: RX +1.00 DS DC X

Date: 06-26-2012
Time: 8:17 AM
Age: 38

GHT
Within normal limits
VFI 99%
MD -0.35 dB
PSD 1.60 dB

Gain
Within normal limits
VFI 98%
MD -0.23 dB
PSD 3.04 dB P < 2%
6 Month FUV OCT
Idiopathic Intracranial Hypertension
Pseudotumor cerebri

VIII.

Ueber Meningitis serosa und verwandte Zustände.

H. Quincke
in Keil.

Zustande. Ztschr Nervenh 1897:9:149-168

About serous meningitis and related conditions
Entry Criteria
Modified Dandy Criteria of IIH

- symptoms and signs of increased ICP
- otherwise normal neurologic exam
- normal level of alertness
- neurodiagnostics normal except elevated ICP
- no other cause of increased ICP present
Undiagnosed Papilledema in a Morbidly Obese Population: A Prospective Study

4 of 647 had subtle optic disc edema (3 had LP with mild elevation)
All 4 had normal VF
Average BMI = 47

Krispel et al. JNO 2011
IIH - Age at Diagnosis

10-19
20-29
30-39
40-49
50-59

Wall and George, Brain 1991
IIH Symptoms
A case control study

Giuseffi et al., Neurology 1991
Neuroimaging in IIH

Empty Sella

Papilledema, Flattened Globes
Unfolded Optic Nerve Sheaths
Lateral sinus stenosis

Sensitivity and specificity of 93% using ATECO MRV in prospective study of IIH.

Farb et al., Neurology 2003
Mechanisms of Visual Loss in IIH

- Axoplasmic flow stasis leading to axonal ischemia at the optic disc
- Spread of edema into macula (seen best with OCT)
- Transient hypotension – watershed infarct
- Choroidal folds (refractive)
- Elevated peripapillary retina (refractive)
Original Investigation

Effect of Acetazolamide on Visual Function in Patients With Idiopathic Intracranial Hypertension and Mild Visual Loss
The Idiopathic Intracranial Hypertension Treatment Trial

The NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee

Main entry criteria

- Age 18 - 60 years
- Meets modified Dandy criteria of IIH
- Newly diagnosed (6 weeks or less)
- Presence of papilledema
- PMD -2 dB to -7 dB in the worst eye
Newly Diagnosed Untreated Participant Eligible for IIHTT meets Dandy criteria for IIH

Perimetric Mean Deviation: from -2 dB to -7 dB

Randomize in IIHTT
n = 165

--- GWAS

Acetazolamide

Placebo

Increase medication to maximum dosage tolerated. Instruct in a low sodium, weight reduction diet.

Monitoring
Automated Perimetry: MD at 6 months

Statistical Comparisons

Is acetazolamide + diet superior to placebo + diet in improving visual field function over six months?

Secondary measures at six months:
- Change of optic disc edema
- Change in quality of life
- Change in CSF pressure
IIHTT

- Secondary aim: GWAS to screen for disease-causing mutations and IIH risk alleles – 154 subjects turned out to be an insufficient sample size to answer the question
- Blood and CSF stored for future studies.
IIHTT Demographics; n = 165

- 161 women / 4 men (2.65%) were enrolled
- Age 29.2 ± 7.5 with range of 18 – 53 years
- 88% were obese; mean BMI was 39.9
- 5% identified family members with IIH
- -2 to -7 dB comprises about 1/3 of IIH patients
IIHTT
CONSORT Diagram

317 individuals were assessed for eligibility
152 Excluded
120 Did not meet eligibility criteria
70 PMD outside eligible range
17 Unreliable visual field testing
5 CSF pressure too low
28 Other
23 Declined to participate
9 Other reasons

165 Randomized
86 Randomized to receive acetazolamide
86 Received acetazolamide as randomized
69 Completed follow-up
62 Continued taking acetazolamide
7 Discontinued study intervention
16 Withdrawn
6 Lost to follow-up
4 Withdrew consent
3 Time commitment
1 Desired active treatment
1 Moved
1 Treatment failure later adjudicated to be performance failure
1 Treatment failure
86 Included in the primary analysis

79 Randomized to receive placebo
79 Received placebo as randomized
57 Completed follow-up
56 Continued taking placebo
1 Discontinued study drug
16 Withdrawn
9 Lost to follow-up
5 Time commitment
1 Adverse event
1 Needed disallowed medication
6 Treatment failure
79 Included in the primary analysis
Treatment Failures (n=7)

All had high grade papilledema at baseline
Symptoms at Baseline

- Headache: 84.2%
- TVO: 67.9%
- Back Pain: 52.7%
- Pulsatile Tinnitus: 52.1%
- Dizziness: 51.5%
- Photophobia: 47.9%
- Neck Pain: 41.8%
- Visual loss: 32.1%
- Nocturia: 29.7%
- Cognitive: 19.8%
- Radicular Pain: 18.8%
- Diplopia: 17.6%
Dosages of study medication at conclusion of study participation

- **Placebo**: 3.5 g/d
- **Acetazolamide**: 2.5 g/d

Average Adherence:
- Acetazolamide: 89%
- Placebo: 93%
Primary Outcome
Variable was Perimetric Mean Deviation (PMD)
What is the perimetric mean deviation?

Perimetric Mean Deviation (PMD) = Average loss per test location weighted for the central points
The prototype defect...
Grades of visual loss in IIH

Grade I

Grade II

Grade III

Grade IV

Grade V

Stages of progression in IIH

Wall and George, Brain 1991
Primary Outcome
Change in PMD in Worst Eye

- Mean Change in PMD (Worst Eye)
- Month

Acetazolamide + diet
Placebo + diet

Multiple Imputation
Rx effect = 0.71 dB
p = 0.05

Last observation carried forward:
p = 0.007
Effect 1.19 dB

Mediation analysis:
ACZ effect independent of weight loss
PMD Effect Size
Frisén grade 3-5 baseline

Effect size = 2.27 dB
p < 0.001

Overall
0.71 dB

Mean PMD at baseline was 3.5 dB
Change in Papilledema Grade
Worst Eye

Grades of Papilledema

0 1 2 3 4 5
Weight Loss – Target 6%

Placebo + Diet  
Acetazolamide + Diet

Effect size -8.93 lbs.

p < 0.001

Mediation analysis showed ACZ effect was independent of weight loss
Improvement in CSF Pressure from Baseline

Effect size -59.9 mm H$_2$O
CI: -96.4 to -23.4 mm H$_2$O

$\ p = 0.002$
Vitamin A results. There is little difference between cases and controls.
Laboratory Values

- Sodium, CBC with diff, LFTs, RFTs – unchanged
- Chloride increased and CO2 decreased with ACZ
- Potassium:

Effect size = -0.23 meq/l
p < 0.001
No K⁺ supplementation

Baseline compared to 6 months
Study Limitations

- Entry criteria of -2 to -7 dB limits generalization
- Modest effect on mean deviation of 0.71 dB
- 19% withdrawal rate
Longitudinal IIHTT (LiihTT)
Surgical IIHTT (SiihTT)

Participant Eligible for SiihTT
Meet Dandy criteria for IH

Perimetric Mean Deviation:
from -8.5 dB to -30 dB

Randomize in SiihTT
n = 216

Acetazolamide → ONSF → CSF Shunt

Increase medication to maximum dose tolerated.
Instruct in a low sodium, weight reduction diet.

Monitoring
Perimetry: SITA 24-2 for six months
Optic disc photos at 6 months

Statistical Comparisons
(based on perimetric mean deviation)

Is CSF Shunting superior to acetazolamide + diet and ONSF + acetazolamide and diet in improving visual field function over six months?

Secondary measures at six months:
Changes in CSF pressure
Papilledema change / OCT changes
Change in quality of life
What have we learned?

- Acetazolamide led to significantly improved:
  - Visual field function
  - Papilledema grade
  - Quality of life measures
  - CSF pressure
- The PMD effect was greatest with high grade edema and was mostly in month 1
- Acetazolamide led to a reduction in TFs (6 vs. 1)
- Acetazolamide was well tolerated at high dosages and was associated with improved QoL
What have we learned?

- Acetazolamide promotes weight loss and its effect on vision is independent of weight loss.
- Acetazolamide used alone does not require K+.
- Perimetry performance failures were not uncommon and need to be recognized.
- Study of pointwise change across the visual field shows generalized changes, most peripherally.
- ETDRS acuity was abnormal more than expected.
Future Issues to be Resolved

- Long term management of PTC patients
  - The LIIHTT study
- Optimal dosing of diamox
- Need for a noninvasive means of assessing ICP
- Optimal treatment for patients with PMD greater than -7 dB (medical, ONSF or shunting)
- Possible role of bariatric surgery for these patients who cannot lose weight or get off Diamox