Rebound Intracranial Hypertension Following Treatment of Spinal CSF Leaks

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Dallas, Texas
### Disclosures (past 2 years):

<table>
<thead>
<tr>
<th>Role</th>
<th>Organization</th>
</tr>
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<tbody>
<tr>
<td>Advisory Board</td>
<td>Alder BioPharmaceuticals, Amgen, Avanir, Biohaven Pharmaceuticals, electroCore, Eli Lilly, <strong>Supernus</strong>, Teva, Zosano</td>
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<tr>
<td>Speaker</td>
<td><strong>Allergan</strong>, Amgen, Avanir, electroCore, <strong>Supernus</strong>, Teva</td>
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<tr>
<td>Consultant</td>
<td>Avanir, Eli Lilly, electroCore, Autonomic Technologies, Inc.</td>
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<tr>
<td>Grant support</td>
<td>Merck</td>
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<td>Support: Clinical trial site PI</td>
<td>Eli Lilly, Autonomic Technologies, Inc, Zosano</td>
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<td>Board of Directors</td>
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<td>Editorial Board</td>
<td>Headache, Neurology Reviews</td>
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<tr>
<td>Contributing author</td>
<td>Medlink Neurology, Medscape</td>
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</table>
Other Disclosures

There are no FDA approved medications indicated for the treatment of (headaches associated with) intracranial hypertension.

Due to limited literature on this subject, much of the content is my opinion based on experience treating patients with the pseudotumor cerebri syndrome (idiopathic intracranial hypertension) and those with rebound intracranial hypertension.
Learning Objectives

• Describe the differential diagnosis of rebound intracranial hypertension
• Develop a rational strategy for headache management in patients with RIH
Case Presentation

46-year-old woman with orthostatic headaches for 10 years
Occurred after being upright for 6-7 hours, 7 out of 10
Top of head, sharp with nuchal aching
Photophobia, constant tinnitus; pulsatile tinnitus in the AM
Daily, constant
Relieved only with sleep and at high altitude
Also with occipital headaches and interscapular tension and burning neck pain
1 year prior she work up two days in a row with a “wet ear” and a halo of blood and clear liquid on the pillowcase
Headaches worsened after this
Evaluation for skull base CSF leak was negative
Started on topiramate 100 mg daily

LP 5 years prior for possible IIH showed OP 150 mm CSF
CT myelogram showed multiple perineural cysts but no leak
Headaches improved for 1 month after non-targeted blood patch
Imaging 2 years prior
PMHx: Ehlers Danlos syndrome

Exam: BMI 28 kg/m²
Normal optic nerves with spontaneous venous pulsations
Normal neuro exam
Trendelenburg test: 7 → 5 out of 10 in 10 minutes
Targeted blood patch of perineural cyst at T10-11 gave short-lived relief

Topiramate discontinued for possible exacerbation of intracranial hypotension

Subsequent blood patches with relief for 5-9 weeks.
Developed a different headache 10 days after her last blood patch
Worse when lying flat
Awakened with headache that resolved 10-15 minutes of being upright, then the previous orthostatic headache began 4 hours later

More history....
Gained 30 pounds after stopping topiramate
“Life long” history of transient visual obscurations when standing
Characteristics of Rebound Intracranial Hypertension (RIH) Headaches

Usually occur within hours to days of epidural blood patch (or surgery)

Headache phenotype is completely different than SIH headache
- Location (often frontal or retro-orbital)
- Orthostatic component disappears
- May be worse upon awakening
- Patients may be unable to sleep flat

Kranz PG et al. AJNR 2014;35:1237-40
Why Does RIH Occur?

1. Overcorrection of SIH (mechanism uncertain)
   Disrupted spinal CSF absorption from blood patch
   Upregulation of CSF production (unlikely)

2. The primary problem was unrecognized intracranial hypertension
   “Self decompression” via spinal CSF leak
   (Optic nerve sheath, sella, skull base leak, spinal leak)
High Pressure Headaches in IIH: IIHTT Headache Characteristics at Baseline (n=165)

HA present in 84% at baseline (70 ACZ, 69 PBO)

Locations of headache:
- Frontal  68%
- Ocular   47% (usually bilateral)
- Nuchal  47%
- Posterior 39%

Characterization of pain:
- Pressure-like  47%
- Throbbing  42%
- Stabbing  5%

Unilateral  30%
Global     36%

Wall M et al. JAMA 2014;311:1641-51
Friedman DI et al. Headache 2017;57:1195-1205
Yunisova G et al. Headache 2017;57:1152-3

ACZ = Acetazolamide, PBO = placebo
IIH-related symptoms

- Constant visual loss (34%)
- Transient visual obscurations (68%)
- Diplopia (22%)
- Dizziness (53%)
- Headache with none of the above (14%)
Migraine associated symptoms were common (86%): Photophobia (70%), phonophobia (52%), nausea (47%), vomiting (17%), worsened with routine physical activity (50%)

<table>
<thead>
<tr>
<th>Headache phenotype (ICHD -3 beta)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>52%</td>
</tr>
<tr>
<td>Tension-type</td>
<td>22%</td>
</tr>
<tr>
<td>Not classifiable</td>
<td>7%</td>
</tr>
<tr>
<td>Probable migraine</td>
<td>16%</td>
</tr>
<tr>
<td>Probable tension-type</td>
<td>4%</td>
</tr>
</tbody>
</table>

Friedman DI et al. Headache 2017;57:1195-1205
Why Does IIH Cause Headaches?

Pain sensitive structures in the brain
- Meninges
- Veins

Increased central venous pressure
Venous sinus stenosis

Central sensitization?
Was IIH the Initial Problem? Clues on History and Exam

Prior diagnosis of IIH/PTCS
Obesity or recent weight gain
Other risk factors for IIH (cyclines, vitamin A, etc.)
Undiagnosed/untreated sleep apnea
History (or symptoms of) prior skull base leak
  CSF rhinorrhea or otorrhea
Other IIH symptoms in the past
  Pulsatile tinnitus

Previous imaging signs of increased ICP
   The opposite of what is seen in SIH:
   Empty sella
   Expanded perioptic subarachnoid space
   Tortuous optic nerve
   Venous sinus stenosis

   Tonsillar descent can occur with high or low pressure
   No other evidence of brain sag
Imaging Abnormalities*

Protrusion of optic nerve papilla into the vitreous, flattening of posterior sclera, expanded and tortuous optic nerve sheath complex

Flattening of posterior sclerae where optic nerve leaves the globe

Expanded/empty sella

*in the appropriate clinical context

Agid R, Farb RI. Minerva Med 2006;97:365-70
Neuro-Ophthalmic Symptoms and Signs

Transient obscurations of vision
Blurred vision
Visual field defects
Binocular diplopia
  Usually horizontal
  Abducens palsy
Loss of previously present spontaneous venous pulsations
Papilledema

Mokri B. Mayo Clin Proc 2002;77:1241-6
Papilledema

Helpful:
Disc elevation, obliteration of optic cup
Peripapillary halo, obscuration of vessels crossing the disc margin

Grade 2
Grade 3
Grade 4
Grade 5
Normal
Treatments

Discontinue caffeine
Low sodium diet
Sleep reclining or sitting, elevate head of bed
Sleep apnea evaluation/treatment as indicated

Therapeutic lumbar puncture
Medical management
  CSF pressure-lowering agents (oral; IV glycerol helpful in one case report of RIH)
  Management of IIH (e.g., weight loss)
Procedural options

Friedman DI. Continuum 2018;24:1066-91
Medical Management of CSF Pressure

**First choice**: Acetazolamide  
Starting dose (adults) 500 mg BID  
Titrate up to 2000 mg BID as tolerated  

**Second choice**: Methazolamide  
Starting dose 25 mg BID  
Titrate up to 100-200 mg BID as tolerated (not renally excreted)  

**Third choice**: Furosemide or bumetanide  

**Fourth choice**: You choose  

**Allergic patient** (no cross reaction with sulfa antibiotics):  
- Triamterene  
- Spironolactone (also good for PCOS)  
- Ethacrynic acid  

*Be careful if combining diuretics!*
Considerations for Headache Treatment

Headache Phenotype - ICHD classification

Location, character of pain, duration, associated features (nausea, photophobia, phonophobia, etc.)

  Migraine
  Tension-type
  Hemicrania continua
Symptomatic Treatment of Headache

Naproxen
Acetaminophen
Other NSAIDs
  Indomethacin may lower ICP
Triptans, dihydroergotamine (migraine phenotype or previous history of migraine)
Avoid butalbital, caffeine
Avoid opioids if possible although may be needed short-term
Antiemetics as needed
Preventive Medications

Headaches at least once a week
Symptomatic medications ≥3 days weekly
Start low, go slow
Leverage possible side effects - many cause weight gain

Silberstein SD et al. Neurology 2012;78:1335-45
Holland S et al. Neurology 2012;78:1346-53
<table>
<thead>
<tr>
<th>Medications</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate, Zonisamide</td>
<td>Weight loss, pCSF lowering effect</td>
<td>Tolerability, Renal stones, Pregnancy</td>
<td>No adverse effect on weight loss in LIHHTT</td>
</tr>
<tr>
<td>TCAs (low dose)</td>
<td>Sleep disturbance</td>
<td>Weight gain with higher doses</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>May lower pCSF</td>
<td>Tolerability</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>No systemic AEs</td>
<td></td>
<td>CM phenotype</td>
</tr>
<tr>
<td>SSRI/SNRI</td>
<td>Co-morbid depression</td>
<td>Possible weight gain</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td>Peripheral edema</td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Worsen depression, Exercise intolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------</td>
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<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td>Riboflavin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unknown:

Devices (neuromodulation)
GCRP targeted treatments
Cannabinoids
Shunting for Headaches in IIH - JHMI

(n=115 procedures)
1 procedure 46%
2 procedures 24%
3-5 procedures 19%
≥6 procedures 12%

95% had HA improvement at one month
Recurrent headache in 48% at 36 months
Revision more common with LP shunts

Transverse Sinus Stenting For IIH (any reason)

Literature Review of 19 studies (207 individuals)
- Inconsistent criteria used for stenting (not all had papilledema)
- Headache and ICP were only universal findings
- Gradients varied and were not always measured

192 patients presented with headache (duration weeks to years)

Headache after stenting
- Complete resolution in 72 (38%)
- Improvement in 83 (43%)
- No change in 35 (18%)
- Worse in 2 (1%)

Long term durability not reported

Teleb MS et al. Interven Neurol 2014;2:132-43
### Summary: Headache and ICP

<table>
<thead>
<tr>
<th>Feature</th>
<th>IIH</th>
<th>SIH</th>
<th>Primary HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Often frontal</td>
<td>Often posterior</td>
<td>Anywhere</td>
</tr>
<tr>
<td>Postural component</td>
<td>Usually none</td>
<td>Often worse when upright</td>
<td>Depends on HA type</td>
</tr>
<tr>
<td>Timing</td>
<td>Morning or no fluctuation</td>
<td>Latter part of day</td>
<td>Patterns vary by HA type</td>
</tr>
<tr>
<td>Nocturnal awakening</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Worse with Valsalva, exertion, bending</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Migrainous associated symptoms</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect of caffeine</td>
<td>None or worse</td>
<td>Improvement</td>
<td>Either</td>
</tr>
<tr>
<td>Effect of high altitude</td>
<td>Worsens</td>
<td>Improves</td>
<td>Often worse</td>
</tr>
<tr>
<td>Trendelenburg</td>
<td>No effect</td>
<td>Often improves</td>
<td>No</td>
</tr>
<tr>
<td>Pulsatile tinnitus</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
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</table>
## Summary: Other features

<table>
<thead>
<tr>
<th>Feature</th>
<th>IIH</th>
<th>SIH</th>
<th>Primary HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsatile tinnitus</td>
<td>Common</td>
<td>Rare (not pulsatile)</td>
<td>May be present</td>
</tr>
<tr>
<td>TVOs</td>
<td>Common</td>
<td>No</td>
<td>No (or &gt; seconds and not postural)</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Usually obese</td>
<td>Often slim or normal</td>
<td>All</td>
</tr>
<tr>
<td>Joint hypermobility</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
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<tr>
<td>Sex</td>
<td>Usually female</td>
<td>Male or female</td>
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<tr>
<td>Neck or back pain</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Radicular pain</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Papilledema</td>
<td>Usually present</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Venous pulsations</td>
<td>Absent</td>
<td>Usually present</td>
<td>Usually present</td>
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Friedman DI. Continuum 2018;24:1066-91
## Summary: Diagnostic Tests

<table>
<thead>
<tr>
<th>Feature</th>
<th>IIH</th>
<th>SIH</th>
<th>Primary HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sella / Pituitary</td>
<td>Empty sella</td>
<td>Enlarged pituitary</td>
<td>Sometimes empty; pituitary enlarges in pregnancy</td>
</tr>
<tr>
<td>Ventricular size</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Tonsillar descent</td>
<td>Possible</td>
<td>Common</td>
<td>Possible</td>
</tr>
<tr>
<td>Flat posterior sclera</td>
<td>Common</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Distended optic nerve sheath complex</td>
<td>Common</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Flat anterior pons</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>LP opening pressure</td>
<td>High</td>
<td>Low, normal or high</td>
<td>Anything</td>
</tr>
<tr>
<td>Post LP headache?</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Improvement of headache with LP?</td>
<td>Often</td>
<td>No</td>
<td>Possible</td>
</tr>
</tbody>
</table>
Back to the Case

- Acetazolamide started was poorly tolerated at the dose needed to help headache (had to take it in the middle of the night) - severe cognitive effects
- Changed to methazolamide, better tolerated but did not work as well
- Added furosemide without benefit
- Several therapeutic LPs helped only briefly
- Patient distraught
Considered options:
- VP shunt
- Optic nerve sheath fenestration
- Stenting
Vision good and not felt to be a good candidate for ONSF
Agreed to avoid shunt because of EDS
Evaluated for a stent and had procedure done

Right transverse sinus stented (and through to be fenestrated rather than having arachnoid granulation)
Pre-procedure gradient 21 mm Hg across stenosis
Post-procedure gradient <5 mm Hg stenosis
Take Home Points

• RIH headache is different than SIH headache and usually begins within hours to days of blood patches
• Therapeutic LP may be enough to relieve symptoms
• First line for medical treatment: acetazolamide or methazolamide
• It is possible for patient with primary IIH to develop cranial and spinal CSF leaks - evaluate patient for evidence of pre-existing IIH
• Headaches are usually self-limited although may take months to resolve
• Surgery is the last option to treat headache alone
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