Idiopathic Intracranial Hypertension Update

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Disclosures…

- I have no disclosures to report.
- I'm not perfect…
- Questions??
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Idiopathic Intracranial Hypertension (IIH)

- Aka: Pseudotumor Cerebri (PTC)
- Defn: increased ICP without a mass effect and with normal CSF composition
- MOA: intracranial venous drainage obstruction ; decreased CSF drainage
- F>>M (90% vs. 10%) ; females of child-bearing age
- Risk factors = obesity (70% of IIH), delayed CSF absorption, venous outflow abnormalities/increased cerebral venous sinus pressure
- *Headaches = 90% of cases
  - Most common Sx
- Blurred vision, loss of VF (up to 96%), visual obscurations, permanent visual loss (25%)
- *Papilledema = most common Sn ; 89-95% of cases

Modified Dandy's Criteria (Revised 2008)

1. Absence of mass lesion or hydrocephalus with CT or MRI
2. Elevated CSF opening pressure upon lumbar puncture with normal CSF profile
   - Non-obese patient >200 mmH2O = Abnormal
   - Obese patient >250 mmH2O = Abnormal
3. Intact neurological exam with the exceptions of visual disturbances, and/or 6th nerve palsy, and/or papilledema

PTC/IIH Symptoms

1. ***Headache** (worse upon awakening) (90%)
2. Transient Vision Loss (62%)
3. Pulsitile Tinnitus (48%)
4. Blurred Vision
5. Vomiting
6. Diplopia

PTC/IIH signs…

- Papilledema! In up 95% of cases! (Puffer et al. 2014)
- "With rare exception, all PTC/IIH patients have papilledema, a hallmark of subacute intracranial hypertension."---Galgano et al. (2013)
- Although papilledema is present in the vast majority of PTC/IIH patients, its absence it not an exclusionary criteria." ---Galgano et al. (2013)

Ocular work-up in IIH…

- Visual Acuity
- **Visual Fields**
- **EOM's**
- **Fundus Exam**

} Most important to assess in IIH

- Retinal Imaging (FP, OCT, etc.)
- Color Vision
- Contrast Sensitivity

Visual Acuity and Color Vision in IIH

- **Visual Acuity:**
- Acuity tests foveal function
- Not typically affected unless edema extends into central 10° of fixation

- **Color Vision:**
- Only been found to be abnormal in ~20% of cases
- Ishihara defects only noted in the existence of moderate to marked visual loss and optic atrophy
- Not the most reliable way to follow patients

EOM's/VF's in IIH…

- EOM's:
- If present, uni/bilateral 6th nerve palsies are present 2° stretching nerve between apex of clivus bone/Dorello's canal and exit zone of 6th nerve on brainstem
- Dilation required in all 6th nerve palsies to rule out/in papilledema per Will's Eye

- Visual Fields:
- *Most important test to follow for changes
- Enlarged blindspot first to show, followed by generalized constriction, and nasal defects.
- Any kind of defect is possible though…

VF's in neuro-optometry…. Is testing the central 30° enough?

- "Humphrey SAP has replaced Goldmann perimetry in clinical practice despite fears that peripheral visual field defects may be missed. This fear seems unwarranted as only 1-2% of patients with nonglaucomatous VF defects have abnormalities in the peripheral field beyond 30° degrees in the absence of central field defect."

- Alternatively said….98-99% of neurological VF defects will show up in the central 30° when tested….pretty good odds!

Kedar S, Ghate D, Corbett JJ. Visual fields in neuro-ophthalmology. Indian J Ophthalmol. 2011;59:103-109

Neuroimaging/workup in IIH…Order is important…why???

1. Order MRI/MRV first

2. Followed by lumbar puncture if MRI/MRV is normal
   - >200 mmH2O in nonobese patients = abnormal
   - >250 mmH2O in obese patients = abnormal

- Herniation through foramen magnum can compress upper medulla which is where the respiratory and cardiovascular centers are located → Death

Van Crevel H, Hijdra A, de Gans J. Lumbar puncture and the risk of herniation: when should we first perform CT? J Neurol. 2002;249:129-137.

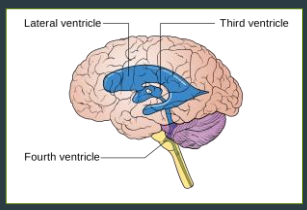
What are we looking for in work up?

- **MRI**
  - Rules out space occupying mass, hemorrhage, etc.
  - Empty sella, pituitary deformities, distention of ON, posterior globe flattening
- **MRV**
  - Rules out transverse sinus stenosis and/or venous sinus thrombosis
- **Lumbar Puncture (LP)**
  - Document elevated opening/intracranial pressure
- **LP cytology**
  - Rule out infectious meningitis, blood, and other possible issues/causes

CSF Hydrodynamics

- Oh crap……you're kidding me right?

Where is CSF made again???

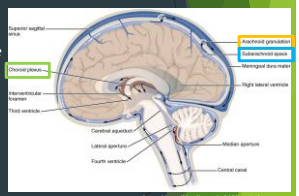


https://commons.wikimedia.org/wiki/File:Diagram_showing_where_the_ventricles_are_in_the_brain_CRUK_387.svg

Answer: Choroid Plexus in Lateral, 3rd, & 4th Ventricles

Where does CSF drain to?

- CSF is absorbed from the subarachnoid space across the arachnoid villi into the venous circulation.
- The arachnoid villi act as one-way valves between the subarachnoid space and the dural venous sinuses. The rate of absorption correlates with the CSF pressure.
  - "Pressure gradient valves"
- Dural Venous Sinus Thrombosis important to rule out with MRV!



https://en.wikipedia.org/wiki/Ventricular_system

Pathophysiology of IIH…

- Any blockage along this CSF drainage pathway or in the venous sinus drainage can result in increased ICP!
- Bottom Line MOA = obstruction of intracranial venous drainage

PTC /IIH Treatment Options…

1. Weight loss (5-10% is sometimes curative!)
2. Carbonic anhydrase inhibitors (6-50% less CSF production)
   - Acetazolamide and/or Topiramate
   - No oral steroids → weight gain
3. Ventricoloperitoneal Shunt / Lumboperitoneal Shunt
   - Headaches only ; vision stable
4. Optic Nerve Fenestration
   - Vision/Visual Field worsening ; no headaches
5. Venous Sinus Stenting
   - In venous sinus stenosis

Topamax vs. Diamox?

- Acetazolamide = CAI inhibitor ; works on ciliary body and choroid plexuses
- Topiramate = novel anticonvulsant with many MOA; epilepsy/migraines
- Sulfonamide drug….be careful of sulfa allergies
- Also has carbonic anhydrase inhibition component; and decreases appetite
  - Weight loss of 5-10% alone may be curative in some cases of IIH
  - Average weight loss of 7.3% was obtained in one year on medication
- Monitor for angle closure glaucoma and myopic shift!!!
  - 85% of this happens within first 2 weeks of therapy
  - Ciliochoroidal infusion occurs
  - MOA = lenticular/uveal effusion and ciliary edema causing forward displacement of the lens-iris diaphragm with resultant narrowing of the anterior chamber.
  - D/c med; cycloplege and IOP lowering meds may be needed. LPI not helpful.

Alore PL, Jay WM, Macken MP. Topiramate, pseudotumor cerebri, weight-loss and glaucoma: an ophthalmologic perspective. Sem Ophthalmol. 2006;21:15-17.

How long should CAI's be maintained?

- Can/Should Tx ever be discontinued once Sn/Sx are under control?
- A long-term follow up study was done in PTC patients using a CAI (acetazolamide) over 6.2 years.
- 54 total patients followed for over 6 years
- 60% of patients experienced multiple recurrent episodes over this time span
- None of the recurrences occurred while maintained on acetazolamide!
- Good evidence to maintain longterm Tx???

Kesler A, Hadayer A, Goldhammer Y, Almog Y, Korczyn AD. Idiopathic intracranial hypertension: risk of recurrence. Neurology. 2004;63:1737-9.

Idiopathic Intracranial Hypertension Treatment Trial (IIHTT)

HHS Public Access

Author manuscript

JAMA. Author manuscript; available in PMC 2015 March 17.

Published in final edited form as:

JAMA. 2014 April 23; 311(16): 1641–1651. doi:10.1001/jama.2014.3312.

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

What was being investigated?

- To determine whether acetazolamide is beneficial in improving vision when added to low-sodium weight diet in patients with IIH and mild vision loss.
- The purpose of the trial was to determine the effect of acetazolamide in reducing or reversing visual loss after 6 months of treatment when added to a weight-reduction program.
- N=165 (86=acetazolamide & diet, 79=placebo & diet)
  - Completed: n=126 (69 vs. 57)
- -2 to -7 dB perimetric mean devation at baseline
- Acetazolamide initial dosage = **500 mg BID PO**
- Increase in 250 mg tablet every week up to 4000 mg/day!!!

Outcomes being measured…

- Primary outcome = change in PMD from baseline → 6 mo in most severe eye
- Secondary outcomes
  - change in PMD from baseline → 6 mo for better eye
  - papilledema grade
  - CSF pressure
  - visual acuity
  - QOL
  - vital signs
  - lab results
  - presence of HA
  - treatment failure

Visual Field Findings…

- Acetazolamide/Diet = 1.43 dB improvement
- Placebo/Diet = 0.71 dB improvement

} Most severe eye

- Acetazolamide/Diet = 0.87 dB improvement
- Placebo/Diet = 0.42 dB improvement

} Better eye

Papilledema Grading…

- Papilledema grade 3-5 = 2.27 dB improvement
- Papilledema grade 1-2 = -0.67 dB improvement
- Significant improvement in acetazolamide groups in study and fellow eyes with FP's
  - QOL improved too
- Weight change
  - -7.50 kg in acetazolamide at 6 mo
  - -3.45 kg on placebo at 6 mo
- CSF Pressure
  - -112.3 mmH20 on acetazolamide at 6 mo
  - -52.4 mmH20 on placebo at 6 mo
- No change in headache severity or visual acuity
  - 69% still had headaches on acetazolamide at 6 mo
  - 68% still had headaches on placebo at 6 mo

Adverse Events

- 9 total patients in study dropped out
- Decreased CO2 levels
- Increased Cl- levels
- Mild decrease in potassium levels (no supplementation needed)
- No changes to sodium
- No liver function changes

- Conclusion:
  - "In patients with IIH and mild visual loss, the use of acetazolamide with a low-sodium weight reduction diet, compared with diet alone, resulted in modest improvement in visual field function. The clinical importance of this improvement remains to be determined."

--- NORDIC IIHTT 2014

Pregnancy Considerations…

- Topamax = FDA Category D; evidence shows up to 10-20% of dose can be found in infants who are nursing
- Acetazolamide = FDA Category C; case reports of placenta crossing ; has been avoided in pregnancy in the past…..new evidence to suggest otherwise?
- If both are avoided in pregnancy, then sometimes repeat LP's may be necessary in short term to keep ICP down; inherent risks…

Lee AG, et al. The use of acetazolamide in idiopathic intracranial hypertension during pregnancy. Am J Ophthalmol. 2005;139:855-9.

National Collaborative Perinatal Project (NCPP) 1959-1974

- "The use of carbonic anhydrase inhibitors (CAIs) has a large pool of human data on which to base clinical decisions. The source is the National Collaborative Perinatal Project (NCPP) conducted by the NIH from 1959 through 1974. This study monitored more than 50,000 mother-child pairs and 1,024 instances of systemic usage of acetazolamide during pregnancy. In the resulting offspring, there were 18 instances of malformations. The predicted number due to chance was 18.06. This suggests that the incidence of malformations from acetazolamide exposure during pregnancy is no greater than the natural incidence. In the same study, there were 12 documented first trimester exposures to acetazolamide. No anomalies were observed in the resulting offspring."

---Steven Odrich, MD (Bronx, NY)

http://www.aao.org/publications/eyenet/200906/letters.cfm?RenderForPrint=1&

Lee et al. The use of Acetazolamide in IIH During Pregnancy. *Am J Ophthalmol*. 2005;139:855-9.

- 12 patients on Diamox 500 mg BID PO during pregnancy
- No adverse side effects nor congenital malformations noted
- Cited the results of the Collaborative Perinatal Project as well

- "In summary, there is no convincing evidence from the literature for the recommendation to limit the use of acetazolamide for IIH in pregnancy. Although the use of acetazolamide might be restricted in the first trimester, this recommendation may have a more medicolegal than medical rationale. It is our recommendation that acetazolamide be considered if the risk of nontreatment (e.g., progressive visual loss) is sufficiently high to warrant its use."

Question to y'all:

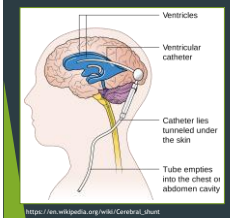
Is it appropriate for O.D.'s to prescribe Diamox for these patients long term???

Surgical Considerations…

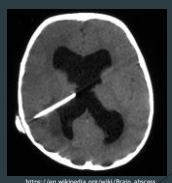
1. Headaches only, vision stable (can be used for both HA's and vision too)
   ----- LP shunt, VP shunt
2. Vision loss/VF worsening despite maximal medical Tx
   ----- Optic Nerve Fenestration
3. Venous sinus thrombosis
   ----- Anticoagulants
4. Venous sinus stenosis
   -----Venous sinus stenting

- Majority can be managed via weight loss and oral meds (Diamox)

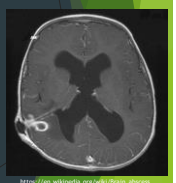
1A) Ventriculo-Peritoneal Shunts (VPS) and Ventriculo-Atrial Shunts (VAS) in IIH



https://en.wikipedia.org/wiki/Cerebral_shunt



https://en.wikipedia.org/wiki/Brain_abscess



https://en.wikipedia.org/wiki/Brain_abscess

1B) Lumboperitoneal shunts in IIH

- L3/L4 or L4/L5 spaces most commonly used
- Drain into peritoneal space like VPS

VPS vs. LPS…

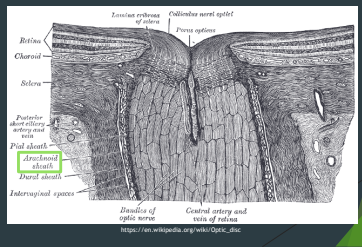
- Ventriculo-Peritoneal Shunt (VPS):
  - Infection rate of 7-15%
  - 20% revision rate q2 yrs
- Lumbar Peritoneal Shunt (LPS):
  - Infection rate of 1%
  - 50% revision rate q2 years

- "In short, most shunted PTC patients require multiple revision surgeries during their lifetime."
  ---Galgano MA et al. (2013)

2) ON Sheath Fenestration…

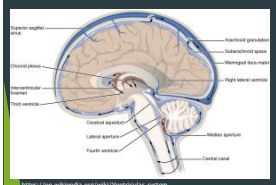
- Defn: make slits in ON sheath to reduce the local pressure around the optic nerves.
- ~50% of unilateral ON sheath fenestration procedures results in resolution of visual symptoms in both eyes.
  - Both optic nerves are connected via the subrachnoid tissue around the optic chiasm
- Typically only done for visual Sn/Sx *without* headaches…
  - If headaches → shunt procedure is better option
- Safe and effective up to 10 years per several studies
- Revision rate is usually very low ; 1 procedure per lifetime generally

Optic Nerve Fenestration

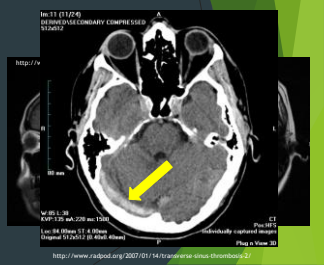


https://en.wikipedia.org/wiki/Optic_disc

3) Dural Venous Sinus Thrombosis



https://en.wikipedia.org/wiki/Ventricular_system



http://www.radpod.org/2007/01/14/transverse-sinus-thrombosis-2/

DVS Thrombosis Considerations…

- Blood clots in young people are NOT normal…
- If DVST occurs, hematological workup and anticoagulant therapy is required.
  ---Subramanian PS et al. (2014)
- Consider: CBC with diff, CMP, lipid panel, PT/PTT, Protein S, Protein C, Homocysteine levels, Lupus anticoagulant, anticardiolipin, Factor V Leiden, Prothrombin mutation, Antithrombin III mutation, Sickledex screen, hemoglobin electrophoresis

DVS Thrombosis Treatment…

- Rule out clotting disorder, infection, etc.
- Aggressive anti-coagulation (heparin, warfarin, clopidogrel)
- Not a candidate for DVS Stenting in vast majority of cases…
- If anticoagulation and oral CAI's do not work, then may need shunt surgery

Dural Venous Sinus Stenosis

Dural Venous Sinus Stenosis (DVSS)

- Defn: focal, narrowed section of dural venous sinuses causing back up/turbulent venous blood flow
- *Most common at junction of Sigmoid and Transverse sinuses
- Not a true blood clot like DVST is…
- Treatment = weight loss, oral CAI, and/or DVS Stenting procedure

DVSS in IIH vs. Normals…

- Focal stenosis has been demonstrated in 90+% of IIH patients using advanced imaging techniques.
- Furthermore, focal stenosis in the same sinus territory was only demonstrated in 6.8% of asymptomatic control subjects.
- Might be on to something here….

4) Dural Venous Sinus Stenting

- Right transverse sinus is dominant in 73% of cases
- MOA: Increases drainage of venous blood from venous sinus system which helps with the pressure dependent valves, arachnoid villi granulations, allowing them to clear CSF in to the venous system more efficiently/quickly → decreasing intracranial pressure
- High frequency of resolved or improved HA's and papilledema with this method

DVS Stenting…

- Not every patient is a candidate for DVS Stenting
- Criteria Needed:
  1. Presence of venous sinus stenosis (MRI/MRV) ; not thrombosis…
  2. Transvenous manometry across the stenosis >10 mmHg differential
- Catheter with stent and manometer placed in femoral vein and "fished" upwards to location of sinus stenosis
- Post-Op Medications:
- Plavix 75 mg x 6-12 weeks then d/c
- ASA 325 mg for life

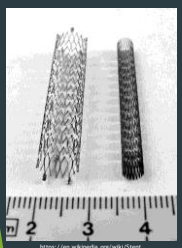
Transvenous Manometry in IIH

- Significant = >10 mmHg pressure differential of proximal vs. distal locations in respect to stenosis

	Pre Stent	Post Stent
Superior Sagittal Sinus	45 mmHg	21 mmHg
Right Transverse	46 mmHg	20 mmHg
Right Sigmoid	15 mmHg	19 mmHg
Difference	31 mmHg	1 mmHg

Lazzaro MA, et al. Neurosurgery. 2012;71:877-83.

Dural Venous Sinus Stenting for IIH



https://en.wikipedia.org/wiki/Stent

Suboccipital/Subtemporal Cranial Decompression

- Very invasive ; but historically pretty successful…
- Remove part of skull to allow for more room inside…
- Not gold standard anymore
- Can be used in severely refractory cases unresponsive to traditional surgical procedures for ICP and IIH

Optometry IIH/PTC Summary…

- Make the diagnosis
- Get MRI/MRV
- Refer for LP
- Neurology should start Diamox/Topamax
- Monitor x 1 month post med Tx, then q3-4 months until resolution/stability (Varies)
- Serial OCT, FP, and HVF's are necessary to gauge Tx/stability
- Relay findings to managing neurologist/PCP regularly.
- Encourage weight loss

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Questions???
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