*Idiopathic Intracranial Hypertension: The Plumbing*

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* Speaker’s Bureau for Boehringer-Ingelheim
* Dr. Ed Neuwelt - Oregon Health and Sciences University
* Blood Brain Barrier Disruption
* Grand Rounds - September 25th
* Mid-annual BBB Meeting
  * 2-5 pm
* History of IIH
* Pathophysiology
* Evaluation
* Treatment
* Shoulders of Giants
* KUMC Experience
* Pseudotumor Cerebri, Pseudotumor Cerebri Syndrome, Primary Pseudotumor Cerebri
* Idiopathic intracranial hypertension
* Intracranial hypertension of unknown cause
* Secondary PTC
  * Atypical patients - males, non-obese women, pre-pubertal children, and those refractory to traditional treatments
  * Vitamin A-induced intracranial hypertension, tetracycline induced intracranial hypertension, steroid withdrawal related intracranial hypertension

* Proposed Naming

1) Wall et al, The Idiopathic Intracranial Hypertension Treatment Trial, JAMA Neurology, June 2014, Vol 71, No. 6
* Internist and Surgeon
* Studied the CSF in dogs and rabbits in 1872 and injected red sulphide of mercury into the subarachnoid space to demonstrate “flussigkeit” or CSF flow
* First described the syndrome in 1893
  * “meningitis serosa”
* 1891 he and Wynter described the first lumbar puncture at the 10th Congress of Internal Medicine in Wiesbaden, Germany
  * First measurement of intracranial pressure

* reported 10 cases (7 women and 3 men)
  * only two women met the current criteria
  * both suffered headache, papilledema, and elevated intracranial pressure with normal CSF composition
  * impaired visual acuity was evident in one
  * postulated an increase in CSF secretion mediated by the autonomic nervous system
  * speculated head injury, stress, excessive alcohol, pregnancy, influenza, and otitis media as possible etiologies

Quincke’s cases

2) Quincke HL. Verhandlungen des Congresses für innere Medizin, Wiesbaden 10, 321-331. And,
* neurologist in Hamburg
* pupil of Erb
* introduced the term “pseudotumor cerebri” in 1904
* reported on 18 patients
* none met the modern criteria
* 27-year-old woman with a 2 year history of suppurative otitis media followed by 2 weeks of headache, dizziness, vomiting, and diplopia
* Bilateral papilledema and a left sixth nerve palsy
* Cerebral abscess was suspected but operative exploration demonstrated a left lateral sinus thrombosis
* She subsequently recovered
* Nonne correctly concluded that she had hydrocephalus secondary to sinus thrombosis caused by otitis media

*Nonne’s patient*
* Syndrome of headaches, visual disturbances (vision loss, blurry vision, diplopia), tinnitus (venous flow disturbances)

* CN 6 palsy
  * courses anteriorly toward the clivus → runs superiorly along the clivus enclosed within Dorello’s canal and pierces the dura inferior to the posterior clinoid process
  * courses over medial petrous apex toward the cavernous sinus
  * its oblique course and relatively fixed anchor in Dorello’s canal makes it prone to stretching when raised ICP

* Papilledema
* Elevated lumbar p
* No evidence of an

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* daily
* typically occur upon awakening
* pressure behind the eyes
* do not have typical migrainous components
  * nausea, vomiting
  * photophobia, phonophobia
* fail traditional treatments
  * migraine medications, opiates
* transient visual loss is the second most common presenting symptom and is the major morbidity
  * typically precipitated by postural changes and can occur several times throughout the day
  * one theory is transient ischemia of the optic disc caused by optic nerve swelling
* typically visual loss is gradual but abrupt onset has been reported and can have a more fulminant course and **less chance of visual recovery**
* diplopia, curtain of vision loss, blurry vision

**Visual Disturbances**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal optic disc</td>
<td>Blurring of nasal and temporal disc borders by overlying nerve fiber bundles in inverse proportion to the disc diameter. Pattern of the peripapillary nerve fiber bundles is strictly radial, without tortuosity. Rarely, a major vessel may be obscured, usually in the upper pole.</td>
</tr>
<tr>
<td>1</td>
<td>Very early papilledema</td>
<td>Excessive blurring of the nasal border of the optic disc, with disruption of the normal radial arrangement of nerve fiber bundles. Normal temporal disc margin. Subtle grayish halo along the circumference of the optic disc, with a temporal gap.</td>
</tr>
<tr>
<td>2</td>
<td>Early papilledema</td>
<td>Elevation of the nasal circumference of the nerve head, and blurring of all of the temporal margin. Halo now surrounds the disc completely.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate papilledema</td>
<td>Elevation also of the temporal circumference, and a clearly increased diameter of the nerve head. The elevated borders now totally obscure one or more segments of the major retinal vessels. The circumpapillary halo has an irregular outer fringe with finger-like extensions.</td>
</tr>
<tr>
<td>4</td>
<td>Marked papilledema</td>
<td>Elevation of the entire nerve head in combination with obliteration of the optic cup, or compression of the cup to a slit, or total obscuration of a segment of the central retinal artery or vein.</td>
</tr>
<tr>
<td>5</td>
<td>Severe papilledema</td>
<td>Anterior expansion of the nerve head now dominates over sideways expansion. Nerve head assumes smooth, dome-shaped protrusion, with a narrow and smoothly demarcated halo. Major retinal vessels climb steeply over the dome surface. Segments may be totally obscured by overlying swollen tissue.</td>
</tr>
</tbody>
</table>

Walter Dandy first proposed diagnostic criteria in 1937:

- Signs & symptoms of increased ICP – CSF pressure >25 cmH2O
- No localizing signs with the exception of abducens nerve palsy
- Normal CSF composition
- Normal to small (slit) ventricles on imaging with no intracranial mass

Described clinical course of 22 patients with this condition over 7 years in the 1920s and 1930s:
- All patients complained of symptoms consistent with IIH
  - Headaches, blurred vision, and vomiting
- Fundoscopy in all cases demonstrated papilledema and in many cases retinal hemorrhages indicative of long-standing severe intracranial hypertension, confirmed by elevated pressures on LP or ventricular tap
- Ventriculography excluded a significant mass lesion in all cases
- Treated with unilateral subtemporal decompressive craniectomy

*J.L. Smith modified them in 1985*

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms of raised intracranial pressure (headache, nausea, vomiting, transient visual obscurations, or papilledema)</td>
</tr>
<tr>
<td>2</td>
<td>No localizing signs with the exception of abducens (sixth) nerve palsy</td>
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<tr>
<td>3</td>
<td>The patient is awake and alert</td>
</tr>
<tr>
<td>4</td>
<td>Normal CT/MRI findings without evidence of thrombosis</td>
</tr>
<tr>
<td>5</td>
<td>LP opening pressure of &gt;25 cmH₂O and normal biochemical and cytological composition of CSF</td>
</tr>
<tr>
<td>6</td>
<td>No other explanation for the raised intracranial pressure</td>
</tr>
</tbody>
</table>

*2001 paper, Digre and Corbett amended Dandy's criteria further
*require exclusion of venous sinus thrombosis as an underlying cause

* In 2002 Friedman and Jacobson derived from Smith’s criteria
* Required the absence of symptoms that could not be explained by a diagnosis of IIH
* Did not require the actual presence of any symptoms (i.e. headache) attributable to IIH
* Require that the LP is performed with patient lying sideways
* Did not insist on MR venography for every patient
  * Only in atypical cases

A Multicenter, Double-blind, Randomized, Placebo-controlled Study of Weight-Reduction and/or Low Sodium Diet Plus Acetazolamide vs Diet Plus Placebo in Subjects With Idiopathic Intracranial Hypertension With Mild Visual Loss

Wall et al, The Idiopathic Intracranial Hypertension Treatment Trial, JAMA Neurology, June 2014, Vol 71, No. 6
* Efficacy of diet (low sodium) vs. acetazolamide (4 gm/day) to reduce or reverse visual loss

* Change in the perimetric mean deviation (PMD) from baseline to 6 months was the primary outcome

* Additional outcomes measured yearly up to 4 years
  * changes in papilledema grade, CSF pressure measurements, other visual field measures, and quality of life measures

* IIH patients with mild visual loss (-2 to -5 dB baseline PMD) enrolled

* Demonstrated improvement in visual function in acetazolamide group

Wall et al, The Idiopathic Intracranial Hypertension Treatment Trial, JAMA Neurology, June 2014, Vol 71, No. 6
* signs and symptoms of increased ICP
* absence of localizing findings on neurologic examination
* awake and alert
* no other cause of increased intracranial pressure
* absence of deformity, displacement, or obstruction of the ventricular system
* absence of abnormal neuroimaging except for empty sella turcica or optic nerve sheath with filled out CSF spaces
* smooth-walled non-flow-related venous sinus stenosis or collapse should lead to another diagnosis*

1) Wall et al, The Idiopathic Intracranial Hypertension Treatment Trial, JAMA Neurology, June 2014, Vol 71, No. 6
2) http://www.jaypeejournals.com/eJournals/ShowText.aspx?ID=3096&Type=FREE&TYP=TOP&IN=._eJournals/images/JPLOGO.gif&IID=238&isPDF=NO
LP opening pressure 20-25 cmH₂O and ≥1 of the following:

- Pulsatile tinnitus
- Cranial nerve 6 palsy
- Frisen grade II papilledema
- Echography for drusen-negative and no other disc anomalies mimicking disc edema present
- MRV with lateral sinus collapse/stenosis
- Partially empty sella on coronal or sagittal views and optic nerve sheaths with filled out CSF spaces next to the globe on T2-weighted axial imaging

IIHTT Modified Dandy Criteria cont’d

Wall et al, The Idiopathic Intracranial Hypertension Treatment Trial, JAMA Neurology, June 2014, Vol 71, No. 6
* Clinical symptoms, elevated LP opening pressure, CTV/MRV

* Abnormalities in CSF hydrodynamics
  * excess production or malabsorption
  * vs.
  * Abnormal dural sinus drainage

* Cerebral venogram with dural sinus manometry delineates cause

* Pathophysiology
Debate as to whether stenosis is primary cause of elevated ICP or due to elevated ICP

Documentation of disappearance of stenosis in transverse sinuses and transverse-sigmoid sinus junctions after shunting or LP by several investigators who argue that stenosis is result of elevated ICP

Bono et al. followed 14 patients with IIH and transverse sinus stenosis and found no change in the anatomical narrowing despite normalization of CSF pressure in 64% of the patients

Two patient populations in IIH
* Those with true idiopathic intracranial hypertension
* Those with intracranial hypertension caused by venous outflow obstruction (secondary)

* Blood drains from confluences of sinuses into the transverse sinuses \(\rightarrow\) rarely in equal amounts

* Right transverse sinus typically drains the superior sagittal sinus and is larger than the left, which drains the straight sinus (deep structures)
* Flow or absorption of CSF is proportional to pressure gradient across the arachnoid villi
* When dural sinus pressure is elevated due to an obstruction or resistance to flow (stenosis), pressure gradient across the arachnoid villi is reversed
* Results in decreased absorption of CSF through this route
* Increased sagittal sinus pressure and increased resistance to flow lead to a concomitant increase in intracranial pressure

*Pathophysiology cont’d*

Stenoses can be seen in 2 morphologic forms

- Extrinsic smooth gradually narrowing tapered stenosis
  - Compression from swollen brain parenchyma

- Intrinsic discrete obstructions (intraluminal)
  - Arachnoid granulations (AG)
    - Sparse in transverse sinuses, mainly in the SSS
    - One study showed right-sided dominance in trabeculae/septa as well as in AG
      - With its larger surface, logical that more AG would be allowed to project into the SSS
  - Fibrous septae
    - Variable sizes were observed, from small ''pillar''-like structures to large broad structures
  - Trabeuclae
    - Thin string-like structures, which are solid yet strong

References:

Central obesity is thought to be a contributing factor.

Results in elevated intra-abdominal, cardiac filling, pleural, and central venous pressure, which all potentially contribute to elevated intracranial venous pressures.

Nadkarni et al looked at two obese middle-aged females who were evaluated for PTC

Dural sinus manometry demonstrated elevated intracranial dural sinus pressure and increased right atrial pressure

Postulated that the elevated right atrial pressures are due to the obese body habitus

These patients underwent bariatric surgery for weight loss

Approximately one year later symptoms of IIH resolved

Repeated dural sinus manometry demonstrated normal pressure gradients

Theory of bariatric surgery is a decrease in right atrial pressure, leading to decreased intracranial venous sinus pressure, and ultimately to lowered intracranial pressure

* Can lead to rapid and substantial weight loss and theoretically reduce ICP

* **Intra-abdominal adhesions** after surgery can make future CSF-diverting procedures (VPS/LPS) more difficult with higher risk of abdominal organ injury

* Unclear benefit to risk ratio
  * All anecdotal evidence

* Bariatric Surgery
* Lumbar puncture
* Neuroimaging
  * CTV, MRV
* Ophthalmologic exam
  * Optical coherence tomography
* Cerebral venogram with dural sinus manometry
* Hypercoaguable testing
Time of Flight imaging used
* First described in 1991 by Huang et al

* Cross-sectional imaging technique that quantitatively assesses multiple layers of retina, allowing measurement of the retinal nerve fiber layer with resolution of approximately 10 µm

* Direct measurements are calculated by a computer algorithm to quantify the nerve fiber layer and total retinal thickness

* Overcomes limitations of conventional photographic imaging in patients with small pupil sizes and nuclear cataracts

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*Goal → symptom relief and vision preservation

*LP - observe for relief with high volume tap (>30 cc CSF)
  * Suggests patient would potentially respond to shunting or stenting

*Patients with mild headaches and stable vision, non-invasive management is often sufficient
  * in obese patients includes weight loss alone

*Anecdotal evidence and small case series have demonstrated that a 6% weight loss resulted in resolution of papilledema

*Medical Management

* acetazolamide (Diamox)
  * carbonic anhydrase inhibitor and diuretic
  * decreases amount of CSF made
  * may also treat symptoms by lowering intra-cardiac right atrial pressures
  * long-term follow up study in IIH patients on acetazolamide demonstrated that 60% of patients experienced multiple recurrent episodes over a mean observation period of 6.2 years
  * none of the recurrences occurred while maintained on acetazolamide

* furosemide (Lasix)
  * Loop-diuretic

* Medical Management cont’d

* topiramate (Topamax)
  * mild carbonic anhydrase inhibitor
  * mild cognitive impairment
* bumetanide (Bumex)
  * loop-diuretic
  * physiological action is to inhibit the mechanism of glial cell volume regulation
  * ventricles in IIH are typically small on radiographic imaging suggesting that alterations in CSF production may not be as significant as alterations in glial cell volume
  * bumetanide may potentially treat IIH by reducing glial cell volume rather than CSF volume

* Serial high volume LPs
  * Effective
  * Limited by patient discomfort, CSF leak, rapid re-accumulation of CSF, difficulty in procedure due to body habitus
  * Preferred in pregnancy with rapid visual deterioration

* 25% will have further visual decline despite medical management and serial LPs

* CSF Diversion
* Ventriculoperitoneal (VPS) or Lumboperitoneal shunting (LPS)
* Small ventricles can be difficult to cannulate with a ventricular catheter using standard techniques
* Accessing the ventricles is possible with stereotactic planning
* LPS is more commonly performed
LPS has a low complication rate and is 80% effective
serious complications are possible but rare
  * paralysis, brainstem herniation, and iatrogenic Chiari-1 malformation
LPS is associated with a lower infection rate (1%) than VPS (7-15%)
LPS has a higher failure rate (50%/2 years for LPS compared to 20%/2 years for VPS) requiring surgical revision
  * Obesity speculated as high failure rate in LPS

*Surgical Intervention cont’d*

“Shunt failure” should be declared only after measurement of ICP

Some patients with IIH do develop chronic daily headaches (VPS, LPS, dural sinus stenting), and this may be mistaken for a malfunctioning shunt or stent

Ventricular size does not routinely change in this patient population with shunt failure

As they started out as normal sized

*Surgical Intervention cont’d*
* Slits in the ONS to reduce local pressure on the optic nerves.
* Theory is that naturally occurring fibrous trabeculations partially block CSF flow between the subarachnoid space and the optic sheath.
  * Reduces transmission of high intracranial pressure to the nerve.
* ~50% of cases unilateral ONSF results in the resolution of visual symptoms in both eyes.
  * Both sheaths are connected at the optic chiasm.
* Does not relieve globally elevated ICP.
  * Headaches, tinnitus, vomiting may still be present.

* Considerable amount of **congenital** asymmetry between transverse and sigmoid sinuses with the right one being dominant up to 73% of the time with hypoplasia or aplasia of the contralateral transverse and sigmoid sinus.

* Symptoms due to dural sinus stenosis (DSS) typically occur when contralateral side is **hypoplastic or aplastic** or co-dominant with bilateral stenoses.

* Brain is predominantly relying on unilateral drainage.

**Endovascular Dural Sinus Stenting (EDSS)**


* Patient has symptoms of IIH
  * Combination of headaches, visual disturbances, tinnitus
  * Elevated LP opening pressure (>25 cmH₂O)
  * Dural sinus stenosis on CTV or MRV
    * 95% sensitivity and 91% specificity of CT/CTV compared to DSA
    * “sensitivity and specificity of MRI/MRV are unknown due to the lack of large MRI/MRV head-to-head studies with DSA”

* Prior to stenting, a diagnostic cerebral venogram with dural sinus manometry is performed under conscious sedation
  * General anesthetics can result in vasodilatation, resulting in falsely low dural pressure measurements

* Microcatheter is advanced to superior sagittal sinus and venogram is performed to visualize the sinuses and area of concern
  * Transverse-sigmoid sinus junction
  * [pics]
Dural sinus manometry
  * Superior sagittal sinus, torcula (confluence of sinuses), transverse sinus, sigmoid sinus, jugular bulb

* Significant pressure gradient across transverse-sigmoid sinus
  * >4-10 mmHg (KUMC >20 mmHg)

* Stenting performed under general anesthesia

* Patient loaded with aspirin 325 mg and clopidogrel 75 mg for 7 days prior to procedure

* If rapid visual loss then procedure may be hastened and faster loading with dual antiplatelet therapy is done

* Clopidogrel inhibition testing is performed
  * Platelet inhibition should be >20%
  * If not then clopidogrel is replaced with prasugrel (Effient)
<table>
<thead>
<tr>
<th>Author Year</th>
<th>n</th>
<th>Sx (%)</th>
<th>Pre MPG</th>
<th>MPG cutoff</th>
<th>Post MPG</th>
<th>Sx Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higgins 2003</td>
<td>12</td>
<td>BMI 37, VO100, P66 H100</td>
<td>18</td>
<td>NR</td>
<td>5.7</td>
<td>VO↑58, P↑42 (33% self resolved), H↑42</td>
</tr>
<tr>
<td>Donnet 2008</td>
<td>10</td>
<td>BMI 27.3, VO100, P100 H100, T90</td>
<td>19.1</td>
<td>NR</td>
<td>NR</td>
<td>VO↑90, P↑100, H↑80, T↑100</td>
</tr>
<tr>
<td>Bussiere 2010</td>
<td>13</td>
<td>BMI 35.9, VO77, P92 H100, T23</td>
<td>22</td>
<td>10</td>
<td>11.25(8)</td>
<td>P↑77, H↑77</td>
</tr>
<tr>
<td>Albuquerque 2011</td>
<td>15</td>
<td>HA100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>H↑80</td>
</tr>
<tr>
<td>Ahmed 2011</td>
<td>52</td>
<td>VO36, P88, H82, T32</td>
<td>20</td>
<td>8</td>
<td>&lt;1</td>
<td>TVO↑100, P↑100 H↑85, T↑100</td>
</tr>
<tr>
<td>Kumpe 2012</td>
<td>18</td>
<td>BMI 31.6, VO94, P89 H66</td>
<td>21.4</td>
<td>NR</td>
<td>2.6</td>
<td>H↑83, P↑93</td>
</tr>
<tr>
<td>Fields 2013</td>
<td>15</td>
<td>BMI 39, P100, H100, T93</td>
<td>24</td>
<td>10</td>
<td>4</td>
<td>P100↑, H↑53 T↑80</td>
</tr>
<tr>
<td>Radvany 2013</td>
<td>12</td>
<td>BMI 32.6, P100 H100, T91</td>
<td>12.4</td>
<td>4</td>
<td>1.25</td>
<td>VO↑91, P↑91, H↑58, T↑91</td>
</tr>
</tbody>
</table>

1 re-stent
6 re-stent
0 re-stent
2 re-stent
KUMC Experience
* Seventeen patients (15 female)
* Mean age 29.47 years
* All had pre-procedural LP with average opening pressure of 38.1 cmH2O (26-55)
* Average pre- and post-intervention pressure gradients were 23.06 mmHg and 1.18 mmHg, respectively
* Pressure gradient change was statistically significant with unpaired t test (p < 0.0001)
* Fifteen (88%) noted improvement in headache
* Fourteen (82%) had visual improvement
* All patients had improvement in their main symptom related to IIH
* Of eleven patients who had follow up OCT, eight improved and three remained stable
* OCT improvement correlated with improved visual acuity
33 year old male with 1 year history of headaches after TBI
- Pressure behind the eyes
- Bilateral papilledema
- LP opening pressure 33 cmH₂O
- 69% stenosis
- 24 mmHg mean pressure gradient
- 0 mmHg post stent mean pressure gradient
• 21 year old female
• Chronic headaches
• Vision loss 1-2 weeks
• Papilledema by optometrist
• LP - OP 36
- 76% stenosis
- 22 mmHg mean pressure gradient
- 0 mmHg post stent mean pressure gradient
* 39 year old female with vision black outs, headaches
* Papilledema
* LP opening pressure 26 cmH₂O
* Tom Whittaker, MD - Neuro-ophthalmology
* Kyle Smith, MD - Neurosurgery
* Jeremy Peterson, MD - Neurosurgery
* Emily Coolbaugh