Pseudotumor Cerebri
and the search for cause

Brian E. McGeeney, MD, MPH
Assistant Professor of Neurology
Neurology Department
Boston University School of Medicine
Search For the Northern Passage

Willem Barentsz
1550-1597
Outline

- Definitions, signs and symptoms
- The role of obesity
- Treatment - medication and interventions
- Venous sinus abnormalities
- Journey of cerebrospinal fluid and the influence of vitamin A and estrogen in the search for cause
History of Pseudotumor Cerebri

Heinrich Quincke (1842-1922)

Max Nonne (1861-1959)
Dandy’s 1937 paper “Intracranial pressure without brain tumour; diagnosis and treatment” described 22 cases, does not list diagnostic criteria, although clearly describes the clinical features of PTCS. All patients recovered. Reported normal ventricular size. ‘Modified Dandy criteria’ from 1985.

Walter Dandy (1886-1946)

1. If symptoms are present, they may only reflect those of generalized intracranial hypertension or papilledema
2. If signs are present, they may only reflect those of generalized intracranial hypertension or papilledema
3. Documented elevated intracranial pressure measured in the lateral decubitus position
4. Normal CSF composition
5. No evidence of hydrocephalus, mass, structural or vascular lesion on MRI or contrast-enhanced CT for typical patients, and MRI and MR venography for all others
6. No other cause of intracranial hypertension identified

## Presenting Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No etiology</th>
<th>Known etiology</th>
<th>total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>59</td>
<td>40</td>
<td>99</td>
<td>90.0</td>
</tr>
<tr>
<td>Disturbance of vision</td>
<td>40</td>
<td>23</td>
<td>63</td>
<td>57.3</td>
</tr>
<tr>
<td>Diplopia</td>
<td>19</td>
<td>20</td>
<td>39</td>
<td>35.5</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>15</td>
<td>20</td>
<td>35</td>
<td>31.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>7</td>
<td>14</td>
<td>12.7</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>10.0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>8.2</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>6</td>
<td>15</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Johnson IH, Paterson A. Brain 1974
Age and Sex Distribution

Age and sex distribution for series of 110 cases of etiology unknown PTCS

Men with PTCS

- Bruce and colleagues studied 721 patients with IIH, 9% were men.
- Men were twice as likely to have severe visual loss.
- BMI known for 67% and no difference between men and women.

Pseudotumor Cerebri Syndrome

Associations

Women
Obesity
Familial
Hypervitaminosis A
Hypovitaminosis A
Tetracyclines
Thyroid disease
Venous obstruction

Endocrine disorders
Sulfa antibiotics
Amiodarone
Growth hormone
Lithium
SLE
HIV
Diagnosis of PTCS
Position and CSF Pressure

- Recent study on the difference in CSF pressure between flexed and relaxed position while recumbent
- 83 patients had LP in flexed lateral decubitus position, pressures also taken in relaxed position
- Mean pressures
  - flexed position: -178.54 mmH₂O
  - relaxed position: -160.52 mmH₂O

Patient TL


Small Ventricular Size in PTCS?

- Huckman (‘76) found normal ventricular size in 17 patients compared to age matched controls.
- Jacobson (‘90) found no evidence of small ventricles in 10 patients compared to 18 controls.
- Reid (1980): ventricular volumes of $1.3\pm 4.9\text{mls}$ (mean $4.9\text{mls}$) in 18 pts compared with $4.5\pm 22\text{mls}$ ($11.7\text{mls}$) in age matched controls.
- Weisberg (‘85) studied 36 pts with PTCS and 10 (36%) had abnormalities on CT, 6 with small ventricles.

100 patients (74 women) underwent LP. All subjects had a normal MRV.

- Overweight and obese subjects did not have abnormal CSF pressure.
- No subject had a CSF pressure >200mmH₂O.

Prospective study on 354 adults with first LP in Neurology Dept. Excluded diagnoses that could be associated with a high CSF pressure, left with 242 adults (45% men)
Median CSF pressures and 95% CI in 4 main BMI groups not greatly different
Regression model based on BMI predicting CSF pressure $r^2 = 0.19$, small

Whiteley W et al. CSF opening pressure: Reference interval and the effect of body mass index. Neurology 2006;67:1690-1691
The Obesity Link

Adipose cells secrete many factors
- Converts inactive cortisone into the active glucocorticoid cortisol
- Aromatase produces estrogens from testosterone, and activity differs depending on site of adipose tissue, likely more active in female adipose distribution

Testosterone \rightarrow estradiol
Androatenedione- \rightarrow estrone
16α-hydroxylated dehydroepiandrosterone- \rightarrow estriol

Meinhardt U, Mullis PE. The aromatase cytochrome P-450 and its clinical impact. Hormone Research 2002. 57;145-152
Medications
- acetazolamide
- furosemide
- Topiramate
- Steroids

CSF Shunts
- Lumboperitoneal shunt
- Ventriculoperitoneal shunt

Optic Nerve Sheath decompression

Treatment of cranial venous Outflow obstruction

Lumbar Punctures

Weight loss

Treatment of cranial venous Outflow obstruction

Weight loss

Treatment of cranial venous Outflow obstruction
**Treatment**

**Medications**
- acetazolamide
- furosemide
- Topiramate
- Steroids

**CSF Shunts**
- Lumboperitoneal shunt
- Ventriculoperitoneal shunt

**Optic Nerve Sheath decompression**

**Treatment of cranial venous Outflow obstruction**

**Lumbar Punctures**

**Weight loss**
Weight Loss and PTCS

- Thought to result in resolution of PTCS in suitable patients
- Increased interest in weight loss, with expanding surgical options for morbid obesity
- Sugarman (1999) described 24 cases of PTCS in obese women who underwent bariatric surgery; 19 followed up, 5 lost to follow up. Of the 19, average weight loss was 100 lbs and all but 1 had resolution of signs and symptoms of PTCS. However 7 of the 19 regained weight and PTCS

CSF Production in the Choroid Plexus

CEREBROSPINAL FLUID
(apical membrane)

CHOROID CELL CYTOPLASM

INTERSTITIAL FLUID or PLASMA ULTRAFLTRATE
Acetazolamide and Diuretics

Acetazolamide clearly reduces CSF secretion and is a primary treatment, but has not been a great success and use varies a lot. No definitive study on the use of acetazolamide. May be used for prolonged periods. MOA may also involve AQP1/4 inhibition. Greer (1968) believed in it did not work and did not use it in a series of 110 cases. Small number of reports on the use of furosemide and oral or intravenous glycerol.

PTCS and Steroids

- After a report by Patterson (1961) steroids were a treatment of choice for PTCS in several centers but there were reports of intracranial hypertension occurring in those on steroids for other reasons, particularly during steroid withdrawal.
- Several studies have demonstrated that steroids cause a substantial reduction in CSF production.
- Response may be as high as 80%.
- More effective in combination with acetazolamide or lumbar punctures.
- Now should limit steroids to those with rapidly deteriorating vision.
- Likely reduces activity of Na\(^+\)-K\(^+\) -ATPase reducing CSF production.

Treatment- Interventions

A Cochrane review on interventions for idiopathic intracranial hypertension noted there were no randomised controlled trials that met criteria, and insufficient information to generate evidence-based management strategy for IIH (last reviewed Feb 2007)

Lueck CJ, McIlwaine GG. Interventions for idiopathic intracranial hypertension. Cochrane Reviews. www.cochrane.org

Brazis PW. Clinical review: the surgical treatment of idiopathic pseudotumor cerebri (idiopathic intracranial hypertension). Cephalalgia, 2008;1361-1373
Optic Nerve Sheath Decompression

- Long history in the treatment of papilledema from any cause (over 100 years)
- Unilateral or bilateral
- Mechanism of action not clear. Possible that a persistent fistula; alternative is that ONSD leads to fibrosis and obliteration of the subarachnoid space around the optic nerve, preventing the transmission of CSF pressure to the nerve itself
- The great majority of eyes will show resolution of papilledema and stabilization or improvement in vision, often in other eye also
- A minority of patients will need further surgery
- Severe visual loss post ONSD have been reported

CSF Shunts

- Lumboperitoneal or ventriculoperitoneal shunts
- Less commonly, cisternal shunting, placed in cisterna magna
- Reliably reduces CSF pressure
- Shunt revisions common, in one series of 269 revisions in 91 shunted patients, average one revision every 2.3 years; Ventricular shunts more likely to be revised.
- Revision due to blockage, low pressure symptoms, infection, and migration
- Lumbar shunts can leak CSF (sc. CSF collection)
- Lumbar shunting may result in symptomatic low pressure, acquired Chiari malformation
### Risk of Recurrence of PTCS

<table>
<thead>
<tr>
<th></th>
<th>Group 1: No recurrence</th>
<th>Group 2: Delayed worsening</th>
<th>Group 3: Recurrence</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Eyes</td>
<td>20</td>
<td>12</td>
<td>6</td>
<td>38</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>White</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>30.5</td>
<td>40</td>
<td>24</td>
<td>32.92</td>
</tr>
<tr>
<td>OP (mm of water)</td>
<td>364 (220-650)</td>
<td>354 (250-550)</td>
<td>376 (280-550)</td>
<td>359 (220-650)</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>9 (81)</td>
<td>5 (83)</td>
<td>3 (100)</td>
<td>17 (85)</td>
</tr>
</tbody>
</table>

## Risk of Recurrence of PTCS

### Table 1 Data on 54 IIH patients

<table>
<thead>
<tr>
<th></th>
<th>Patients with one episode, n = 33</th>
<th>Patients with more than one episode, n = 21</th>
<th>Total, n = 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>29 (87.9)</td>
<td>19 (90.5)</td>
<td>48 (88.9)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>29.3 ± 8.8</td>
<td>30.1 ± 9.4</td>
<td>29.6 ± 9.0</td>
</tr>
<tr>
<td>Obesity</td>
<td>31 (93.9)</td>
<td>18 (85.7)</td>
<td>49 (90.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (12.1)</td>
<td>4 (19)</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>CSF opening pressure, mm H₂O</td>
<td>375 ± 104</td>
<td>343 ± 75</td>
<td>363 ± 95</td>
</tr>
<tr>
<td>Reduced visual acuity during last examination</td>
<td>None</td>
<td>3 (14.3)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Duration of therapy, mo</td>
<td>17.5 ± 11.8</td>
<td>12.3 ± 11.9</td>
<td>13.9 ± 11.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.04 (Mann-Whitney)</td>
</tr>
<tr>
<td>Constriction/rasal fields defects on first examination</td>
<td>8/33 (24.2)</td>
<td>6/21 (28.5)</td>
<td>14/54 (25.9)</td>
</tr>
<tr>
<td>Optic atrophy on last examination</td>
<td>3/33 (9.1)</td>
<td>2/21 (9.5)</td>
<td>5/54 (9.3)</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD.

King (1995) and others reported a high prevalence of venous outflow pathology thought the primary problem but King (2002) then used venography and manometry before and after CSF drainage, retracting earlier conclusions, now suggesting stenosis was due to the high ICP as venous hypertension resolved with CSF removal.
Venous Sinus Abnormalities

Lee and Brazis (2000) failed to show venous abnormalities in 22 prospective young obese women with IIH, by MRV. However Farb (2003) found ‘substantial bilateral sinovenous stenoses’ in 27 of 29 patients with IIH compared with 4/59 controls (21 women, 8 men)

Higgins (2003) looked at 20 pts with PTCS and 40 controls; in PTCS there were bilateral transverse flow gaps in 13 (65%) and none in the controls

Actual incidence depends on how you look for the abnormalities

Donner studied 10 consecutive refractory patients with IIH. All patients had DRCV and manometry of cerebral venous system and had evidence of obstruction.

CSF pressure range 31-59 mmH$_2$O, all had papilledema and 5/10 had pulsatile tinnitus.

All patients had stenting.

Direct Retrograde Cerebral Venography (DRCV)
Endovascular Treatment

After stenting 6 patients had no headache, 2 were improved and 2 unchanged.

Papilledema and tinnitus resolved for all patients

Stent patency was evaluated at 3 months by DRCV and MRV, and 12 months by MR or CTV; all patent

Normalization of CSF and sinus pressures

The Journey of CSF

- The majority of CSF is produced by the choroid plexus epithelium and is not a simple ultrafiltrate.
- Choroidal blood flow is 10 times higher than brain relative to mass.
- Ependyma also produces CSF.
The microscopic arachnoid villi and macroscopic granulations are herniations of the arachnoid membrane into the dural venous sinuses of the brain. Several studies have failed to observe arachnoid villi/granulations in the human fetus. In two microscopic studies of autopsy specimens no arachnoid villi or granulations were observed before birth.

At or around the time of birth, arachnoid projections start to become visible in the dura.

How is CSF drained in the neonatal period?
The Journey of CSF

Lymphatic drainage ~50% of CSF drainage in rats, sheep and rabbits
Arachnoid sheaths of the olfactory nerves, penetrate the cribriform plate
In larger mammals, the capacity for nasal lymphatics and arachnoid villi to drain CSF seems about equal

Appears a significant volume of CSF transport occurs into extracranial lymphatics vessels in adults

Frank H Netter, MD

The Journey of CSF

Spinal CSF Absorption

Studies have shown that radioactive substances move upward when injected into the lumbar region—thought to be bulk flow but this has been questioned. Other explanation—diffusion!

Spinal CSF absorption through arachnoid granulations/villi suggested. Spinal CSF clearance has been demonstrated in sheep and cats to account for 25%-50% of the total CSF absorption.

Edsbagge and colleagues demonstrated spinal CSF absorption in 34 healthy adults, with radionucleotide techniques.

Estimated that the 38% +/- 20% of the CSF absorption in resting individuals and 76 +/- 25% in active individuals was from the spinal subarachnoid space.

CSF Infusion Studies

Consistently demonstrated increased resistance to CSF absorption in studies from 1973

Ahlskog and O’Neill (1982) found absorption defects in 14 of 16 pts; (the 2 exceptions one in remission and the other had a subtemp. decompression)

Gjerris (1985) found abnormality low CSF conductance in 12 of 14 patients, with normal values after starting treatment

Janny (1981) demonstrated resistance to flow in all 16 patients studied with PTCS

*All reported studies have consistently shown an abnormality of CSF absorption usually of considerable magnitude*


Vitamin A and Pseudotumor Cerebri

There is good clinical evidence linking hypervitaminosis A and PTCS
Medications including isotretinoin, etretinate and the leukemia drug all-trans-retinoic acid

The relationship of vitamin A to PTCS is complex; both hyper and hypo-vitaminosis A are associated with PTCS, the majority of the literature concerning hypervitaminosis A

There is a strong association with hypo-vitaminosis A and raised CSF pressure in non human studies, as summarized by Millen and Woollam, 1958. (pigs dogs, calves, lambs)

Vitamin A and Pseudotumor Cerebri

- Warner studied vitamin A levels in CSF in three groups, those with PTCS, those with raised ICP from other causes and those with normal ICP; there was a significantly higher concentration of vitamin A in the CSF of those with PTCS only.

- Calhoun, using ventriculo-cisternal perfusion technique, demonstrated that the cause of increased CSF pressure was impaired CSF absorption. There was some evidence that the impaired absorption was associated with structural changes in and adjacent to arachnoid villi.

- Hayes found fibrosis of the interstitium of arachnoid villi of calves with hypo-vitaminosis A with increased collagen.

Aquaporins are water permeable channels, increasing plasma membrane osmotic water permeability

- Aquaporin-1 (AQP1) in choroid plexus epithelium
- AQP4 is the main water channel in the brain
- AQP4 is strongly expressed at the borders between brain parenchyma and major fluid compartments- astrocyte foot processes (BBB), glia limitants (brain-subarachnoid CSF) and ependymal cells (brain-ventricular CSF)
Evidence that some aquaporins are influenced by estrogen:

- Carreras showed that expression of hepatocyte AQP8 water channels as well as canalicular membrane water permeability is downregulated by estrogen; note the link between estrogen and membrane permeability.

- Branes demonstrate that expression of AQP9 in the oviductal epithelium varied depending on ovarian signals.


Altered Permeability of Endothelium/Epithelium by Estrogen and Vitamin A

- Retinoic acid effects endothelial cell function and influences the composition and functional properties of their underlying extracellular matrix.
- Estrogen has recently been shown to decrease tight junctional resistance and remodeling of occludin, hence estrogen modulation of paracellular permeability.
- Estrogen shown to induce retinoid acid synthesis.

Gorodeski GI. Estrogen decrease in tight junctional resistance involves matrix-metalloproteinase-7-mediated remodeling of occluding. Endocrinology 2007;148;218-231
Paige K et al. Retinol-induced modification of the extracellular-matrix of endothelial cells-its role in growth control. In vitro cellular & Developmental Biology 1991; 27;151-157
Li, XH et al. Estrogen Directly Induces Expression of Retinoic Acid Biosynthetic Enzymes, Compartmentalized between the Epithelium and Underlying Stromal Cells in Rat Uterus. Endocrinology 2004;145:4756-4762
CSF Journey and PTCS

- Choroid Plexus Epithelium (tight junctions)
- Ependyma
- Capillary: gap junctions
- Astrocytes process; BBB
- Interstitial fluid in BRAIN
- AQP4
- Pia
- Arachnoid sleeve of cranial nerves
- Spine
- Venous Sinuses
Conclusions

- Pseudotumor cerebri (IIH) has been a well recognized syndrome for many decades and most patients do reasonably well.
- The leading complication is visual loss.
- Unfortunately the underlying mechanism is not known.
- An excess of CSF volume is not apparent.
- Etiology likely a disorder of altered absorption of CSF, possibly under the direct or indirect influence of female sex hormones.
- Patients are best followed with formal visual fields, not just headache.
- There are no randomized clinical trials on treatment.