Diagnosis and Management of the Pseudotumor Cerebri syndrome in Children. 
A critical review.

Toronto 2014
Daniel Tibussek, MD

Disclosures

• none
Two Germans, Two Revolutions

1891

1851

Overview

• Nomenclature
• Definition
  – „Normal“ values of CSF opening pressure
  – Other diagnostic difficulties
• Epidemiological and clinical data Germany
  – IIH as an incidental finding
  – IIH without papilledema
• Cases report
  – Diagnostic difficulties
• Concluding thoughts
Pathophysiologie

Review Article

Pseudotumor Cerebri Pathophysiology

Brian E. McGovern, MD, MPH; Deborah I. Friedman, MD, MPH, FAAN

Headache 2014;54:445-458

Nomenclature
What’s in a name

- Quincke 1897 „seroese Meningitis“
- Symonds 1931 "otitic hydrocephalus"
- Benign Intracranial Hypertension
- Pseudotumor Cerebri
- Idiopathic Intracranial Hypertension
- Pseudotumor cerebri Syndrome/Komplex


Nomenclature confusion

“This variation in nomenclature reflects the continuing uncertainty about the precise nature of the condition…”

“…an uncertainty also quite clearly reflected in the variations in ideas of origin and treatment”

Pseudotumor cerebri syndrome/complex

- Takes into account that differences between "idiopathic" and "secondary" intracranial hypertension are somewhat arbitrary
- Association with underlying illnesses in up to 77.7% of pediatric patients with "idiopathic" PTC

Tibussek et al. Childs Nerv Syst 2010;26:313-21

Associations with intracranial hypertension

Medical Conditions:
- Hypothyroidism/hyperthyroidism
- Dobry's developmental insufficiency
- Hypoparathyroidism/hyperparathyroidism
- Polyactic acid syndrome
- Chronic anemia
- Vitamin D deficiency

- Uniparental disomatism (Casey 21, Turner syndrome)
- Cystic fibrosis (mainly secondary to associated nutritional problems)
- Systemic lupus erythematosus

Drugs:
- Anticonvulsants
- Antidepressants
- Antihypertensives
- Antineoplastics
- Antipsychotics
- Antischizophrenics
- Anticonvulsant
- Corticosteroids therapy or withdrawal
- Cyclosporine
- Antihistamines
- Phenothiazine
- Lithium
- Vitamin A analogues and estrogen

Definition

What is Pseudotumor Cerebri in the 21. Century?

Definition of Pseudotumor cerebri

- A. Papilledema
- B. Normal neurologic examination except for cranial nerve abnormalities
- C. Neuroimaging: Normal brain parenchyma
- D. Normal CSF composition
- E. Elevated lumbar puncture opening pressure

Definition of Pseudotumor cerebri

- A. Papilledema
- B. Normal neurologic examination except for cranial nerve abnormalities
- C. Neuroimaging: Normal brain parenchyma
- D. Normal CSF composition
- E. Elevated lumbar puncture opening pressure
- BUT: what is elevated opening pressure?


What is the „normal“ CSF opening pressure in childhood?

- Many pediatric textbooks stated an abnormal opening pressure (OP) in children is greater than 20 cm H2O
- Often no references or cross-referencing
- No studies had systematically defined the value for an abnormally elevated OP in children
Methods

- 2 year prospective study at Children’s Hospital of Philadelphia
- Patients undergoing LP as part of their routine clinical care were recruited
  Ages ≥1-18 years of age
Outcomes

• Primary Outcome: OP (cm H2O)
• Study variables:
  • 1) age
  • 2) BMI
  • 3) depth of sedation
  • 4) sedation medication
  • 5) needle size

Opening Pressure Distribution (N = 197)
Limitations

- Subjects cannot be considered “normal”
- LPs performed by many different physicians
- Different sedation regimens
- Still: relatively low number of patients
- Pediatric BP percentiles are based on > 80,000 patient visits!!
Diagnostic Criteria for Pseudotumor Cerebri Syndrome

- Elevated lumbar puncture opening pressure (≥250 mm CSF in adults and ≥280 mm CSF in children)
- [250 mm CSF if the child is not sedated and not obese]

Diagnostic Criteria for Pseudotumor Cerebri Syndrome

• Elevated lumbar puncture opening pressure (>250 mm CSF in adults and >280 mm CSF in children

CLINICALLY NOT HELPFUL AT ALL.
VERY POOR SUPPORTIVE EVIDENCE!


CSF opening pressure measurement

A technique prone to confounders
„normal“ values

Cerebrospinal Fluid Opening Pressure in Children: Experience in a Controlled Setting

Marcus W. Lee MD, Vettakikoru V. Vedanarayanan MD
Department of Pediatric Neurology, University of Mississippi Medical Center, Jackson, Mississippi

• Friedman et al: “in a properly performed lumbar puncture”

Lee and Vedanarayanan. Pediatric Neurology 2011; 45:238-240

What is „controlled setting“?

What About Leg Position?

• Numerous textbooks recommend that the legs must be straight to avoid false elevation of OP.

Brief Communication

Patient Position During Lumbar Puncture Has No Meaningful Effect on Cerebrospinal Fluid Opening Pressure in Children

Robert A. Avery, DO,⁎,†,‡,§ Raleesh D. Mistry, MD,⁎
Samir S. Shah, MD, MSCE,⁎,†,‡,§ Jan Boswinkel, MD,⁎
Jenny W. Huih, MD,⁎ Michael D. Ruppe, MD,⁎
Santiago Borasino, MD,⁎ Daniel J. Licht, MD,⁎
Jeffrey A. Seiden, MD,⁎ and Grant T. Liu, MD⁎

OP in Flexed vs. Extended Position

- Flexed 25.1+9.2 cm H2O
- Extended 24.4+8.4 cm H2O
- In 92.4% opening pressure measurements had less than a 5 cm H2O difference
How about sedation?

LP in PSA. German data.

29 patients (47%) did not receive any kind of PSA

Tibussek et al. Klin Padiatr 2012; 224: 40–42
Does it matter?

Advantages of LP in PSA

- Prevents pain (and pain related elevation of pressure)
- Prevents anxiety/panic/trauma (repeated LP likely!)
- Higher success rate!!
- Comparability better if same PSA regime used
But

• Literally all strategies of sedation/analgesia have the potential to alter the CSF opening pressure!
• The effect is almost unpredictable
• Role of depth of sedation?
• Role of hypercapnia?
• Role of the drugs used?

Ketamine and OP

• Ketamine has long been suspected to contribute to a rise in ICP
• Avery et al. found no statistically significant relationship between ketamine use and OP (n=15!)
• Controversy continues among neurointensivists
LP under sedation

- …should be standard
- …should be standardized

>> guideline?

In order to get routine, LP pressure measurement should generally be done more often.

!Pressure variability in 1 h!

- Bilateral transverse sinus stenosis
- Initial LP Opening pressure < 20cm

*Cephalalgia* 2010 30:1419-25
Remember!

Deborah I Friedman:
„A high opening pressure in and of itself is neither specific nor diagnostic and must be used in context with other data from the history, examination, neuroimaging and laboratory to arrive at the correct diagnosis“

Cephalgia 2010; 30:1415-16

Germany-wide Pseudotumor Cerebri Study
Study details

• Recruiting period: January and December 2008
• Active hospital-based surveillance on paediatric PTC in the German population
• All German pediatric clinics were asked to report all new cases of paediatric IIH to the German ESPED study centre ((German Surveillance Unit for Rare Diseases in Childhood))
• Questionnaires were sent out to get clinical details

Inclusion criteria

• Pseudotumor cerebri was defined as:
  – Age < 18 years
  – Documentation of increased CSF opening pressure ( > 20 cm H 2O)
  – Normal CSF composition (cell count, protein, sugar)
  – Normal cerebral imaging (except “empty sella”)
  – Normal neurological exam except for cranial nerves.
Incidence Germany

• 2008: 61 pediatric cases per year
• \( \approx 0,5/100.000 \) children/year

Previous data
• Incidence general population:
  Ca. 1 per 100,000 /y
• Incidence ♀ 20-44 yrs:
  19 /100,000 ♀ /y

Estimated UK annual incidence is 0.8 (1.0 for girls, 0.5 for boys) per 100,000 child population aged 1-16 years.
However…

Subgroup analysis

- 13 patients had an opening pressure < 28 cm H$_2$O
- This represents 18% of the total PTC study population
- 11 of these had papilledema
Are these cases pseudotumor cerebri???

After careful review

- 9 out of 11 patients with papilledema and CSF opening pressure < 28 cm H₂O had additional signs and symptoms to convincingly support the diagnosis of Pseudotumor cerebri.
- We suggest to label these patients as „probable PTC“ and treat as PTC.
- We believe that in clinical reality there is NO cutoff value for normal CSF opening pressure.
The concept of „probable IIH“

1) If symptoms present, they may only reflect those of generalized intracranial hypertension or papilledema.
2) If signs present, they may only reflect those of generalized intracranial hypertension or papilledema.
3) CSF opening pressure may be < 20 cm H2O
4) Normal CSF composition
5) No evidence of hydrocephalus, mass, structural, or vascular lesion on MRI and/or MR venography
6) Exclusion of other causes of intracranial hypertension
7) Clear clinical response to initial pressure release and/or treatment


More epidemiology

Age/Sex

-10 -5 0 5 10

0 - 3
3 - 6
6 - 9
9 - 12
12 - 15
15 - 18

♂
♀
Female vs Male

In the IIH Treatment Trial (IIHTT) of adult IIH patients, women account for approximately 97% of cases.

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<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
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<tbody>
<tr>
<td>N=61</td>
<td></td>
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<tr>
<td>prepubertal (N=32)</td>
<td>15 (53.1%)</td>
<td>17 (46.9%)</td>
</tr>
<tr>
<td>pubertal (N=29)</td>
<td>20 (68.9%)</td>
<td>9 (31.1%)</td>
</tr>
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</table>

Obesity male
Clinical manifestation

1) IIH as incidental finding
2) Headache
3) IIH without papilledema
IIH as incidental finding

- Germany: 5 von 61 Kinder

„An apparent lack of symptoms does not rule out chronic increased intracranial pressure in young children.“

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Early eye symptoms

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<tr>
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<tr>
<td>∑</td>
<td>32</td>
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</tr>
<tr>
<td>Papilledema</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Abducens nerve palsy</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Stereo vision</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Colour vision</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Visual field</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Eye pain</td>
<td>1</td>
<td>6</td>
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<tr>
<td>No papilledema</td>
<td>6</td>
<td>5</td>
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Approx. 20%
Abducens nerve palsy?
Think Pseudotumor cerebri

Does IIH without Papilledema exist?

„idiopathic intracranial hypertension (IIH) without Papilloedema“ (IIHWOP)
SHORT REPORT

Idiopathic intracranial hypertension: is papilloedema inevitable?

E Wraige, C Chandler, K R E Pohl

Arch Dis Child 2009; 94: 233-236

Germany-Studie: „IIHWHOP“?

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Opening pressure</th>
<th>Signs and symptoms</th>
<th>Headache</th>
<th>Other</th>
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<td>0,6</td>
<td>32</td>
<td>Vomiting, Bulging fontanelle, Sunset phenomenon</td>
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<td></td>
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<tr>
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<td>4,8</td>
<td>37</td>
<td>Abducens nerve palsy</td>
<td>+</td>
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<tr>
<td>♂️</td>
<td>7,0</td>
<td>?</td>
<td>Abducens nerve palsy, visual loss</td>
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<td>♀️</td>
<td>7,3</td>
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<tr>
<td>♀️</td>
<td>12,2</td>
<td>38</td>
<td>-</td>
<td>+</td>
<td>Path. Sono N. opticus</td>
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<td>39</td>
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<td>-</td>
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<tr>
<td>♀️</td>
<td>13,1</td>
<td>45</td>
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After critical review

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<td>Bulging fontanelle,</td>
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IIH without papilledema does exist even after infancy!

However, diagnosis should be critically questioned in these cases!

“a multichambered and subdivided tubular system with a blind end (cul de sac) behind the ocular globe.”

The Papilledema Problem
„False diagnosis of papilledema and IIH“

• 18 children referred with disc swelling and suspected IIH.
• Following a tertiary ophthalmological review: papilloedema was excluded in 10.

• In these 10 children, five had a mean opening pressure on lumbar puncture of 27.2 cm H2O, range 19–32


„Light at the end of the tunnel of the blind leading the blind?“

„Thus, for every child that truly has IIH, I typically see four or five other children without IIH

but with CSF pressure measurement between 17 and 27 cm of CSF“

Colin Kennedy (Editorial) Dev Med Child Neur 2006;48:83-83
LP pressure measurement and eye investigation frequently lead to false diagnosis of Pseudotumor cerebri
Role of cerebral imaging

Accuracy of brain imaging in the diagnosis of idiopathic intracranial hypertension

P.J. Maralani *, M. Hassanlou b, C. Torres *, S. Chakraborty *, M. Kingstone *, V. Patel b, D. Zackon b, M. Bussiere a,c

Results

• N=43

1. Partially empty sella (specificity 95.3%, p<0.0001)

2. Flattening of the posterior globes (specificity 100%, p<0.0001)

3. Combined stenosis score CSS<4 (specificity 100%, p<0.0001)

were highly specific for IIH.
Low sensitivity!

- However, absence of these signs did not exclude a diagnosis of IIH.

  Clinical Radiology 67 (2012) 656-663

- Needs to be confirmed in pediatric population

intraocular protrusion of optic nerve
optic nerve sheath distension

flattening of posterior globe
In the absence of papilledema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if B–E from above are satisfied, and in addition at least 3 of the following neuroimaging criteria are satisfied:

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<tr>
<td>i. Empty sell</td>
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<tr>
<td>ii. Flattening of the posterior aspect of the globe</td>
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<tr>
<td>iii. Distention of the peripapillary subarachnoid space with or without a tortuous optic nerve</td>
</tr>
<tr>
<td>iv. Transverse venous sinus stenosis</td>
</tr>
</tbody>
</table>


Optic nerve ultrasound and intracranial pressure

Therapy and therapy guidance.

How do we decide and why?

Case: Therapy resistance?

- 7 yrs, boy,
- subjective visual disturbance since 6 wks
- Papilledema (Papille prominent, disc margin blurred, R>L)
- Normal visual acuity, visual fields OK
- OP 37 cm H2O
- 4 wks Acetazolamid 10 mg/kg, no adverse effects, BE – 8.4
- No visual disturbances any more

- after wks: 35 cm H2O, eyes did not change
- Plus Furosemid: significant side effects
- E-mail to Dr Tibussek:
  „Doctors talk about VP-shunt“
Sir William Osler, 1st Baronet (born July 12, 1849 – December 29, 1919) was a Canadian physician and one of the four founding professors of Johns Hopkins Hospital (Wikipedia).

Therapy: Controversies

- Medication: (when, what, how long?)
- Monitoring: How? How long?
- Re-LP to control pressure?
- What is therapy-resistence?
- When and which invasive therapy?
- Role of sinus venous stenosis? >> Stent in children?
- When consider bariatric surgery
Acetazolamide, the evidence

"Since no trials met the inclusion criteria no studies were assessed for quality, no data were collected and no analysis was undertaken."

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.

• No significant treatment effects were noted with respect to headache disability (HIT-6 total score)
What are our treatment goals?

1) Maintain/regain normal visual function

With good interdisciplinary work and good drug adherence realistic goal in > 90% of pediatric patients.
Level of evidence: German „expert opinion“

2) Relieve headaches

3) (prevent invasive therapies)

Step-wise approach

• Step 1: correct potentially causal factors (medication, anaemia, hypothyroidism, ..)

• Step 2: LP with CSF drainage to lower pressure >> measure post punctual pressure („closing pressure“)
Pressure release as the only therapy

"Interestingly, **it is not uncommon** to observe a lasting clinical remission after a single lumbar puncture in some IIH patients"

Germany study
- **14/61 Patients** got LP pressure as the only treatment. In 1 case successfully as serial LP.


---

Sinus venous stenosis
Before          After

LP

Therapy-Escalation: When and Why?

"Corbett and Thompson have emphasized that treatment decisions should not rest on ... the severity of papilledema, or CSF opening or closing pressure."

"Instead, the modern management of pseudotumor cerebri is based largely upon the level of visual loss."


Headache as criteria for success?

"Many IIH patients have persistent headaches, even after normalization of the intracranial pressure"

"Patients with IIH frequently have headaches not necessarily related to increased intracranial pressure"

Friedman DI, Rausch A. Neurology 2002; 58:1551-1553
Step-wise approach

Step 3: No visual loss:
- Symptomatic headache (migraine) therapy
- Weight reduction, correct other secondary causes
- **If necessary Acetazolamide**

Step 4: Mild visual loss:
- Acetazolamide
- Furosemide
- (Topiramate)
- Weight reduction, if necessary

Liu et al. 2011 in: Neuro-Ophthalmology, Diagnosis and Management, Saunders, Elsevier

Invasive therapy

- **Step 5: Severe, or progression of visual loss**

  **Always critically question your diagnosis before even considering!**

- High-dose IV steroids and acetazolamide
- Lumboperitoneal shunt for failed ONSD or intractable headache
- Bariatric surgery
Back to the case…

8 months later:
„The eye doctor now questions the diagnosis of PTC. Ultrasound suggests drusen.“ Fluorescence confirmed it

This child did NOT have PTC!

Beware: Our eyes are „subjective“
Neuroophthalmology

- Papilledema: Photo-documentation!
- Visual field (how?)
- Optical Coherence Tomography
- Colour vision
- Contrast sensitivity
- Ultrasound (Drusen)
- …

The so called „therapy resistance“

Without visual disturbances no escalation of therapy!

Exception: worsening papilledema

LP control: do not do routinely!
Often unreliable in children!

Non-Compliance

• Düsseldorf:
  2 Patients with Non-Compliance
  1 x optical atrophy (adolescent)
  1 x VP-Shunt

• Israel:
  „visual outcome was less favorable in pubertal patients“
  due to drug adherence problems?


Therapy resistance?
CAVE: Think of the unlikely!

Spinal Arachnoidal Cyst

The complex mechanisms of CSF circulation

C) Invasive Therapy

• FIRST:
  DO NO HARM!

• SECOND:
  WHAT IS YOUR TREATMENT GOAL?
Interdisziplinary decision!

- Optimal management of IIH requires good communications between specialties to protect the patient from unnecessary lumbar punctures and CSF diversion surgery on the one hand and avoidable visual loss on the other.

Take Home Messages

- The doubtless diagnosis of PTC is difficult!
- Therapy escalation follows visual function monitoring.
- Critically question whether invasive procedure is really unpreventable.
- Critically question diagnosis in any atypical case.
- Interdisciplinary approach!
- Many open questions!
- Do research!