Pseudotumor Cerebri Syndrome: Where is the evidence?

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NO FINANCIAL DISCLOSURES
Nomenclature

- 1897: Quincke reported the first cases of IIH after introduction of the LP
- 1904: named pseudotumor cerebri
- 1940s: cerebral angiography added to pneumocephalography for diagnosing cerebral mass lesions
- 1955: Foley named it benign intracranial hypertension
- 1980s: studies described a high incidence of visual loss with decreased QOL – not “benign”
  - Idiopathic Intracranial Hypertension
DIAGNOSIS
2002 Modified Dandy Criteria for diagnosis of Idiopathic Intracranial Hypertension

<table>
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<tr>
<th>Criteria</th>
<th>Details</th>
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<tr>
<td>Symptoms of raised ICP (headache, nausea, vomiting, transient visual obscurations, or papilledema)</td>
<td>Absence of symptoms that cannot be explained by IIH</td>
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<td>No localizing signs with the exception of reversible cranial nerve palsies with no other identifiable cause (sixth most common)</td>
<td>The patient is awake and alert</td>
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<td>Normal CT/MRI findings, without evidence of thrombosis</td>
<td>LP opening pressure, in lateral decubitus position, of &gt; 25 cmH\textsubscript{2}O and normal biochemical and cytological composition of CSF</td>
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Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children.
Friedman DI; Liu GT; Digre KB

- “IIH” only appropriate for primary intracranial hypertension of unclear etiology
- Those with identifiable secondary cause need etiology specific treatment
- Recommend use of the umbrella term Pseudotumor Cerebri Syndrome (PTCS)
Pseudotumor Cerebri Syndrome (PTCS)

- Primary PTC = IIH
- Secondary PTC = raised ICP from identifiable cause
  - Venous sinus thrombosis
  - Medications
  - Medical conditions
Table 2  Diagnostic criteria for pseudotumor cerebri syndrome

1. Required for diagnosis of pseudotumor cerebri syndrome

A. Papilledema

B. Normal neurologic examination except for cranial nerve abnormalities

C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used

D. Normal CSF composition

E. 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]) in a properly performed lumbar puncture

2. Diagnosis of pseudotumor cerebri syndrome without papilledema

In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if B-E from above are satisfied, and in addition the patient has a unilateral or bilateral abducens nerve palsy

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:

   i. Empty sella

   ii. Flattening of the posterior aspect of the globe

   iii. Distention of the perioptic subarachnoid space with or without a tortuous optic nerve

   iv. Transverse venous sinus stenosis

A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis.
Clinical Course

- Highly variable clinical severity and course

- In most, symptoms resolve with diagnostic LP, medical treatment and weight loss (self limited)

- Some have a chronic course with delayed worsening and recurrence
  - Relapse rate 10-38%

- Fulminant IIH = rapidly progressive symptoms of raised ICP with severe visual loss

Papilledema: Visual prognosis

- 96% have visual field defect
  - Usually mild
  - Patient usually not aware
- Up to 25% develop secondary optic atrophy with permanent visual loss
- 8-10% blind in at least one eye
- Most with severe visual loss have fulminant course or delayed diagnosis.

References:
- Wall M, George D. Brain 1991; 114:155-180
- Wall M. Neurol Clin 2010; 28:593-617
- Digre KB. BMJ 2010; 341:c2836
- Ball AK, Clarke CR. Lancet Neurology 2006; 5:433-442.
Chronic papilledema
RISK FACTORS FOR PTCS & WORSE VISUAL OUTCOME
Obesity

- Over 90% of IIH patients are obese
- Higher BMI associated with higher risk of IIH
- BMI ≥ 40: severe papilledema; more severe visual loss
- Marked recent weight gain a/w poor visual outcome
- Non-obese: risk if recent weight gain of even 5-15%
- Recurrence of IIH ~ higher BMI than initial diagnosis

*Morbidly obese patients need close monitoring for progression of visual field loss

Men have worse prognosis

- 10% with IIH are men
- Similar BMI
- Older at presentation
- Less frequent headache
- Visual prognosis is worse
  - Odds of severe visual loss double
  - Need more aggressive treatment if visual loss present
- Need close follow up

Digre KB, Corbett JJ. Arch Neurol 1988; 45:866-872.
Race

- No difference in incidence
- Black patients have worse visual prognosis (in the US)
  - 3x more likely to have severe visual loss in one eye
  - 5x more likely to be blind in both eyes
  - More aggressive disease
    - Need closer f/u and earlier intervention
- Caucasians: US worse than French

Anemia

- Worse visual outcome
- Prompt treatment of anemia can result in dramatic improvement of vision and disc edema
- Even patients untreated for raised ICP may improve with correction of anemia

Obstructive sleep apnea

- Associated with IIH
- Unclear if independent factor or due to obesity
- May have worse prognosis

Medications that precipitate PTCS

- Tetracyclines (minocycline)
- Cyclosporine
- Lithium
- Nalidixic acid
- Nitrofurantoin
- Danaxol
- Indomethacin; Rofecoxib
- Cimetidine
- Retinoic acid derivatives
  - Acne medications
- Vitamin A derivatives
  - Cod liver oil
- Oral contraceptives
- Levonorgestrel
- Tamoxifen
- Withdrawal from corticosteroids

Tend to have a good prognosis with self-limited course once offending medication is discontinued.

Medical conditions that may cause or worsen PTCS

- SLE
- HTN
- Iron deficiency anemia
- Ulcerative colitis
- Sickle cell disease
- Cystinosis

Ball AK, Clarke CE. Lancet Neurol 2006; 5:433-442.
Factors associated with worse visual outcome in IIH

- Male gender
- Race (black patients)
- Morbid obesity
- Marked recent weight gain
- Anemia
- Obstructive sleep apnea
- Acute onset of symptoms and signs of raised ICP (fulminant IIH)
- High grade papilledema
- Lack of headaches
- Lack of ophthalmology care/oversight
Treatment

- No evidence-based treatment guideline

- Current treatments used (without proven efficacy in large scale randomized controlled trials):
  - Weight loss (diet & exercise)
  - Acetazolamide (diuretics)
  - Repeated LP
  - ONSF = optic nerve sheath fenestration
  - CSF shunting procedures (VP & LP shunt)
  - Controversial: venous sinus stenting
Diuretics

- Acetazolamide = carbonic anhydrase inhibitor
- Decreases CSF production (lower ICP), as well as aqueous production in the eye (lower IOP)
- 20% of patients will fail weight loss + medical therapy

NORDIC = neuro-ophthalmology research
disease investigator consortium
IIH Treatment Trial

- Current ongoing multicenter randomized controlled clinical trial

- Goals:
  - Evidence-based therapy aimed at restoring and protecting vision
    - Follow patients up to 4 years to observe treatment outcomes
    - Determine the cause of IIH: SNPs
Participant Eligible for IIHTT
meets Dandy criteria for IIH

Perimetric Mean Deviation:
from -2 dB to -5 dB

Randomize in IIHTT
n = 154

Acetazolamide

Placebo

Increase medication to maximum dose tolerated. Instruct in a low sodium, weight reduction diet.

Monitoring
Perimetry: SITA 24-2 for six months
Optic disc photos at 6 months

Statistical Comparisons
(based on perimetric mean deviation)

Is acetazolamide + diet superior to placebo + diet in improving visual field function over six months?

Secondary measures at six months:
Change in CSF pressure
Change on optic disc edema
Change in quality of life
IIHTT

- Specific genome studies using single nucleotide polymorphisms
  - > 50 candidate genes for obesity
- Vitamin A metabolism in blood and spinal fluid
- Obesity hormone

- Preliminary data will be presented at NANOS 2014 meeting