Normal Pressure Hydrocephalus: The Evidence

Diagnosis and Treatment

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Disclosures

• Chief Evidence-based Medicine Methodologist
  American Academy of Neurology

• Associate Editor for Level-of-evidence Reviews
  *Neurology*

• Editorial board *Neurology Now*
Objectives

Understand the evidence relevant to the diagnosis and treatment of NPH and apply it to your practice.

Become more comfortable with interpreting effect sizes using a 2 x 2 table.
My conclusions may be different from that of the AAN Guideline

Neurology 2015; 85:2063-2071
Overview

• Background
  • History
  • Pathophysiology

• Diagnosis
  • CSF Tap Test
  • External Lumbar Drain
  • Radionuclide Cisternography
  • Other CSF parameters
  • Clinical features

• Treatment
History

• First described in 1965 by Hakim and Adams

• Condition characterized by
  • the clinical triad
    • gait disturbance
    • urinary incontinence
    • memory impairment
  • Normal CSF pressure on lumbar puncture
  • Radiologic finding of enlarged cerebral ventricles
  • Improvement after ventricular shunting
  • Emphasized as a potentially reversible cause of dementia

Idiopathic NPH
- Unknown cause

Secondary NPH
- Complication of subarachnoid hemorrhage or infectious meningitis

Estimated prevalence of 5.5/100,000

Normal CSF flow
Hydrocephalus

Non-communicating

Communicating
Psuedotumor Cerebri

“Increased flow resistance in arachnoid villi or increased dural sinus pressure”
Different severities to the impedance to flow

\[ P_v \gg P_{sas} \]
\[ P_v > P_{sas} \]
\[ P_v \gg P_{sas} \]

Lesser degrees of impedance to flow: less elevation in pressure
Normal Pressure Hydrocephalus is
Very Chronic Communicating Hydrocephalus
The Syndrome: Selective vulnerability

Gait apraxia
Incontinence
Memory problems
Overview

• Background
  • History
  • Pathophysiology

• **Diagnosis**
  • CSF Tap Test
  • External Lumbar Drain
  • Radionuclide Cisternography
  • Other CSF parameters
  • Clinical features

• Treatment
The diagnostic dilemma

Gait, Cognitive problems and Brain atrophy are frequent...

When is it NPH?
What is a good Reference Standard?

Improvement with shunting

For patients with suspected NPH are there clinical or laboratory features that identify patients who are more likely to improve with shunting?
Literature Search

Inclusion criteria:
- Cohort studies
- Case-control studies
- Case series
- English-language publications

Exclusion criteria:
- Case reports, editorials, meta-analyses, review articles, duplicative reports
- Examined only secondary NPH
- <10 patients with iNPH/suspected iNPH
- Used no comparison group
- Followed patients for response to therapy for <3 months


440 abstracts → 36 articles

Risk of Bias Rated: Class I to Class IV
<table>
<thead>
<tr>
<th>Internal Validity</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Low</td>
</tr>
<tr>
<td>Class II</td>
<td>Moderate</td>
</tr>
<tr>
<td>Class III</td>
<td>High</td>
</tr>
<tr>
<td>Class IV</td>
<td>Very high</td>
</tr>
</tbody>
</table>
Distribution of Measured Effect Sizes by Class of Study (box & whisker)
Class I: Masked Prospective Cohort Study

Recruit Pts w/ suspected NPH

Test

Pos

Neg

Shunt

Evaluate Response

Better

Not Better
Patient recruitment

“In all studies, the authors considered patients candidates for inclusion if they had all or part of the clinical triad, brain imaging studies demonstrating ventriculomegaly, and no history of factors that could cause secondary hydrocephalus.”
Overview

• Background
  • History
  • Pathophysiology

• Diagnosis
  • CSF Tap Test
  • External Lumbar Drain
  • Radionuclide Cisternography
  • Other CSF parameters
  • Clinical features

• Treatment
The European iNPH Multicentre Study on the predictive values of resistance to CSF outflow and the CSF Tap Test in patients with idiopathic normal pressure hydrocephalus

Carsten Wikkelso, 1 Per Hellstrom, 1 Petra Margarete Klinge, 2 Jos Th J Tans, 3 on behalf of the European iNPH Multicentre Study Group


Class I: Masked Prospective Cohort Study

- Recruit Pts w/ suspected NPH
- Test
  - Pos
  - Neg
- Shunt
- Evaluate Response
  - Better
  - Not Better

![Diagram of study design](image)
Suspected NPH Patients recruited

- Mandatory criteria (115)
  - Gait disturbance at onset
  - Mild to moderate cognitive impairment at onset or after gait disturbance
  - Symmetrical quadri-ventricular enlargement
- Additional criteria for “Typical NPH” (67)
  - Typical gait disturbance
  - MMSE > 21, no aphasia or agnosia
  - No infarcts on MRI

Outcome Measures: iNPH Scale

- Gait
  10 meter walk test
- Neuropsychology
  - Grooved Pegboard test
  - Stroop Test
- Balance
  ordinal scale I to VII
- Continence
  Ordinal scale I to VI

Total Score

\[ 2 \times \text{Gait} + \text{Neuropsych} + \text{Balance} + \text{Continence} \]

5

CSF Tap Test

• Baseline testing 24 hours before LP
• 50 ml of CSF removed at 09:00h
• Three hours after drainage baseline testing repeated
• Response: mean of the percent change in all motor and psychometric tests compared with baseline
• 5% considered a positive test
Shunt

• Adjustable ventriculoperitoneal shunt (Codman & Shurtleff)
• Opening pressure set to 120 mm H2O.
• Patients re-examined 1 month to ascertain the patency of the shunts:
  • examination of gait
  • CT scan or MRI
  • ± shunt function test
Primary Outcomes

• Differences between preoperative and 12 month scores on the iNPH Scale and mRS.
• Improvement
  • Increase on iNPH Scale of ≥ 5 points
  • Decrease in mRS of ≥1
Shunt Response by Tap Test: Results

<table>
<thead>
<tr>
<th>Parameter label</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>52%</td>
</tr>
<tr>
<td>Specificity</td>
<td>59%</td>
</tr>
<tr>
<td>Positive PV</td>
<td>88%</td>
</tr>
<tr>
<td>Negative PV</td>
<td>18%</td>
</tr>
</tbody>
</table>

“The CSF TT can be used for selecting patients for shunt surgery but not for excluding patients from treatment.”
“[The] CSF TT can be used for selecting patients for shunt surgery but not for excluding patients from treatment.”

• Patients are either selected (offered surgery) or excluded (not offered surgery)
• If the CSF TT is positive, offer surgery.
• If the CSF TT is negative, offer surgery.
• Why do a CSF TT?
Class I: Masked Prospective Cohort Study

Recruit Pts w/ suspected NPH

<table>
<thead>
<tr>
<th>Tap Test</th>
<th>Shunt</th>
<th>Evaluate Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td>142</td>
<td>Better 51</td>
</tr>
<tr>
<td>115</td>
<td></td>
<td>Not Better 7</td>
</tr>
<tr>
<td>Neg</td>
<td>142</td>
<td>Better 41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not Better 10</td>
</tr>
</tbody>
</table>

- Tap Test positives: 142, 115
- Tap Test negatives: 142

Evaluate Response:
- Better: 51, 41
- Not Better: 7, 10
## Shunt Response by Tap Test: Raw Numbers

<table>
<thead>
<tr>
<th>Shunt Response</th>
<th>Tap Test</th>
<th>Yes</th>
<th>No</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>51</td>
<td>7</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>47</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>98</td>
<td>17</td>
<td>115</td>
</tr>
</tbody>
</table>
# Shunt Response by Tap Test: Margins

<table>
<thead>
<tr>
<th>Shunt Response</th>
<th>Tap Test</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>51</td>
<td>7</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>7</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Negative</td>
<td>Yes</td>
<td>47</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>7</td>
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</tr>
<tr>
<td>Total</td>
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<td>98</td>
<td>17</td>
<td>115</td>
</tr>
</tbody>
</table>
# Shunt Response by Tap Test: Margins

<table>
<thead>
<tr>
<th>Tap Test</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>51</td>
<td>7</td>
<td>58</td>
</tr>
<tr>
<td>Negative</td>
<td>47</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>85%</td>
<td>15%</td>
<td>100%</td>
</tr>
</tbody>
</table>
### Shunt Response by Tap Test: Prognostic Perspective

**Tap Test**

<table>
<thead>
<tr>
<th>Tap Test</th>
<th>Yes</th>
<th>No</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>51</td>
<td>7</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>47</td>
<td>10</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>85%</td>
<td>15%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Difference:**
6% more of the patients with a positive TT improved with shunting (95% CI -8% to 19%)
Shunt Response by Tap Test: Diagnostic Perspective

<table>
<thead>
<tr>
<th>Shunt Response</th>
<th>Tap Test</th>
<th>Yes</th>
<th>No</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>51</td>
<td>7</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>47</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Yes/No</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Youden’s Index: 11% more of the patients who improved with shunting had a positive TT (95% CI -14% to 33%)
Diagnostic Accuracy: Tap Test

Sensitivity vs. Specificity

- Tap test
- Indifference

Graph shows the relationship between sensitivity and specificity for the tap test, indicating its diagnostic accuracy.
CSF tap test and outcomes

Change in iNPH scale score after tap test vs. Change in iNPH scale score after 12 months
The probability of responding to the shunt is essentially the same whether or not the Tap Test is positive

Risk Difference:
6% more of the patients with a positive TT improved with shunting (95% CI -8% to 19%)

Improvement:
Positive TT: 88%
Negative TT: 82%

Improvement on the CSF TT is probably NOT useful for identifying patients who are more likely to respond to shunting
CSF Tap Test: All Studies

Risk Difference with 95% Confidence intervals

- Wikkelso 2013
- Ishikawa 2012
- Walkenbach 2001
- Malm 1995
- Haan 1988
- Wikkelso 1986

Patients with Neg TT do better
Patients with Pos TT do better
Bayesian Meta-analysis

Risk Difference with 95% Confidence intervals

Patients with Pos TT do better

Patients with Neg TT do better
Conclusion

In patients with suspected iNPH, the TT probably does not identify patients who are more likely to respond to shunting.

Different from AAN conclusion
Overview

• Background
  • History
  • Pathophysiology
• Diagnosis
  • CSF Tap Test
    • External Lumbar Drain
  • Radionuclide Cisternography
  • Other CSF parameters
  • Clinical features
• Treatment
One Class III Study: Un-masked Prospective Cohort Study

<table>
<thead>
<tr>
<th>Recruit Pts w/ suspected NPH</th>
<th>ELD</th>
<th>Shunt</th>
<th>Evaluate Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos</td>
<td></td>
<td>Better</td>
</tr>
<tr>
<td></td>
<td>Neg</td>
<td></td>
<td>Not Better</td>
</tr>
</tbody>
</table>

Permanent improvement after shunt by permanent improvement after ELD

![Graph showing the relationship between improvement in paces after 3 months and improvement in paces after ELD. The graph has a correlation coefficient of r = 0.833 and p < 0.01.]
Shunt Response by ELD: Conclusion

<table>
<thead>
<tr>
<th>Parameter label</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>94%</td>
</tr>
<tr>
<td>Specificity</td>
<td>40%</td>
</tr>
<tr>
<td>Positive PV</td>
<td>84%</td>
</tr>
<tr>
<td>Negative PV</td>
<td>67%</td>
</tr>
<tr>
<td>Risk difference</td>
<td>51% (0.1% to 80%)</td>
</tr>
<tr>
<td>Youden’s Index</td>
<td>34% (-1% to 71%)</td>
</tr>
</tbody>
</table>
Pos ELD Test

Neg ELD Test

Positive PV 84%
Negative PV 67%

Risk Difference

Improved
Not Improved
Diagnostic Accuracy: TT and ELD

Sensitivity vs. Specificity

- Tap test
- ELD

Indifference line

0% to 100% on both axes.
Conclusion
(Single Class III study, large magnitude of effect)

In patients with suspected iNPH, improvement after ELD might identify patients more likely to respond to shunting.

Different from AAN
Overview

• Background
  • History
  • Pathophysiology

• Diagnosis
  • CSF Tap Test
  • External Lumbar Drain
  • Radionuclide Cisternography
  • Other CSF parameters
  • Clinical features

• Treatment
Radionuclide Cisternography


40% of Healthy Controls had abnormal studies
Conclusion (Only Class IV studies)

There is insufficient evidence to determine whether patients with suspected iNPH and persistent ventricular stasis on radioisotope cisternography would respond to shunting.
Overview

• Background
  • History
  • Pathophysiology

• Diagnosis
  • CSF Tap Test
  • External Lumbar Drain
  • Radionuclide Cisternography
  • Other CSF parameters
  • Clinical features

• Treatment
Other CSF parameters

- CSF Pressure
- CSF pressure wave amplitude
- B-waves: slow rhythmic oscillations in intracranial pressure
- \( R_0 \): CSF outflow resistance during infusion test
- MRI Aqueduct
  CSF Flow
Change in CSF pressure with heart beat

Diagnostic Accuracy CSF Parameters

![Diagram showing the sensitivity and specificity of different CSF parameters. The parameters include Tap test, ELD, CSF puls hyper, Pooled Ro, and Pooled MRI aq. The graph illustrates the accuracy of these parameters with data points indicating the percentage of sensitivity and specificity for each test.]
Overview

• Background
  • History
  • Pathophysiology

• Diagnosis
  • CSF Tap Test
  • External Lumbar Drain
  • Radionuclide Cisternography
  • Other CSF parameters
    • Clinical features

• Treatment
Typical vs Questionable NPH

• The diagnostic accuracy of both tests was the same for patients with typical and “questionable” iNPH.

• The outcome after shunting was the same in both typical and “questionable” groups.

Mandatory criteria
• Gait disturbance at onset
• Mild to moderate cognitive impairment at onset or after gait disturbance
• Symmetrical quadri-ventricular enlargement

RESEARCH PAPER
The European iNPH Multicentre Study on the predictive values of resistance to CSF outflow and the CSF Tap Test in patients with idiopathic normal pressure hydrocephalus
Co-morbidities (1 Class III study)

<table>
<thead>
<tr>
<th></th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td>Hypertension</td>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral vascular occlusion</strong></td>
<td>Aortofemoral bypass; stent; internal carotid artery stenosis</td>
<td></td>
<td>Peripheral vascular occlusion</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td>Posterior circulation insufficiency</td>
<td>Vascular encephalopathy; TIA; RIND</td>
<td>Cerebral infarct</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>Arrhythmia; valvular disease; heart failure (coronal); stent; aortocoronary bypass; infarction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, 66% of patients with iNPH had a good response, but 83% of those with low comorbidity index score had a good response
Overview

• Background
  • History
  • Pathophysiology

• Diagnosis
  • CSF Tap Test
  • External Lumbar Drain
  • Radionuclide Cisternography
  • Other

• Treatment
Question

For patients with iNPH does shunting compared to no shunting improve outcomes

- Gait
- Continence
- Cognition
Control

Randomize

Retain

Blind

Primary Outcome

Allocate

Recruit

Rx

No Rx

Follow

Assess

Natural History
Regression to the mean

Selection bias

Attrition bias

Placebo effect
Performance bias
Measurement bias

Reporting Bias

Worse
40%
60%

Better
10%
90%
## Controlled Studies of the Effectiveness of Shunting

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Masking</th>
<th>Follow-up (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahlon 2007</td>
<td>Non-random</td>
<td>Open Label</td>
<td>6</td>
<td>Improved Gait %</td>
</tr>
<tr>
<td>Razay 2009</td>
<td>Non-random</td>
<td>Open Label</td>
<td>3-4</td>
<td>No walking Aid %</td>
</tr>
<tr>
<td>Kazui 2015</td>
<td>Random</td>
<td>Open Label</td>
<td>3</td>
<td>Improved mRankin %</td>
</tr>
</tbody>
</table>

Three Class III Studies
### Improvement by Treatment Status: SIPHONI 2

<table>
<thead>
<tr>
<th>Shunt</th>
<th>Yes</th>
<th>No</th>
<th><strong>Improved</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>32</td>
<td>17</td>
<td><strong>100%</strong></td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>42</td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

**Risk Difference:**
60% more of the patients with a shunt improved.
(95% CI 43% to 73%)
The image shows a bar chart comparing the outcomes of patients with and without a shunt. The chart is divided into two categories: No Shunt and Shunt.

For the No Shunt group:
- Positive PV: 65%
- Negative PV: 95%

For the Shunt group:
- Positive PV: 65%
- Negative PV: 95%

The chart indicates a risk difference between the two groups, with a higher percentage of patients with a positive PV not improving compared to those without a shunt.
Comparative studies of shunting in iNPH
Risk Difference of Improvement

Kahlon 2007

Razay 2009

SINPHONI 2015

Summary

Favors No Shunting

Favors Shunting
### Evidence Synthesis

**Model:** Random Effects  
**Scale:** Linear  
**Effect values less than 0 favor Comparator**

<table>
<thead>
<tr>
<th>Population</th>
<th>patients with iNPH, shunting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>no shunting</td>
</tr>
<tr>
<td>Comparator</td>
<td>improving function</td>
</tr>
</tbody>
</table>

**Important effect size:** 0.100  
**Unimportant effect size:** 0.010

<table>
<thead>
<tr>
<th>Include</th>
<th>Study (Author Year)</th>
<th>Class</th>
<th>Indirectness</th>
<th>Effect</th>
<th>LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kahlon 2007</td>
<td>III</td>
<td>Minor</td>
<td>0.595</td>
<td>0.351</td>
<td>0.748</td>
</tr>
<tr>
<td>1</td>
<td>Razay 2009</td>
<td>III</td>
<td>Minor</td>
<td><strong>0.274</strong></td>
<td>-0.063</td>
<td>0.537</td>
</tr>
<tr>
<td>1</td>
<td>SINPHONI 2015</td>
<td>III</td>
<td>Minor</td>
<td>0.608</td>
<td>0.432</td>
<td>0.730</td>
</tr>
</tbody>
</table>

| Summary (Rand. Effects) | III | Minor | 0.532 | 0.364 | 0.700 |

**Conclusion (moderate confidence):** For patients with iNPH, shunting is probably more effective than no shunting in improving function.
Bayesian Synthesis of comparative studies of shunting in iNPH
Risk Difference of Improvement
Benefits vs Risk

- Short-lived improvement?
  - Decreased response to shunting after 6 months
  - Fewer than half of patients were considered to be improved in iNPH symptoms after 18 months

- Complications
To Shunt or Not to Shunt

**Benefits**
- Unknown Magnitude and duration of benefit

**Risks**
- Complications: Subdural
Conclusions

- Do not consider the diagnosis in a patient without both clinical and radiographic features consistent with NPH
- Do not rely on a CSF tap test for the diagnosis
- An external lumbar drain might identify patients more likely to respond to shunting
- Shunting in the appropriately selected patient is probably beneficial—the magnitude and duration of the benefit is unknown
- Shunting increases the risk of subdural hematoma
- We need a well done randomized, masked trial
Normal Pressure Hydrocephalus: The Evidence

Diagnosis and Treatment

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