Normal-Pressure Hydrocephalus (NPH)

PATHOPHYSIOLOGY

NPH - communicating hydrocephalus with increased resistance to CSF outflow (at subarachnoid space or arachnoid villi) and normal ICP (absence of headache & papilledema).

- normal ICP is maintained as result of apparent compensations.
- ICP is not always normal - transient ICP elevation may increase ventricular size and new fluid balance is reached with normal pressure but with higher force, based on Pascal's law of pressure in fluids.

Causes of subarachnoid space-arachnoid villi obstruction / scarring:

1) SAH
2) meningitis
3) head trauma
4) CSF protein↑

N.B. large number of patients do not have identifiable cause (idiopathic NPH).

PATHOLOGY

- there are no generally accepted neuropathological criteria for postmortem diagnosis.
- discrete abnormalities, such as arachnoid fibrosis, occur too infrequently.
CLINICAL FEATURES

- older patient with insidious PROGRESSIVE TRIAD (in order of appearance):

  N.B. patients may appear mildly parkinsonian, but their tremor, if present, is postural, not resting.

N.B. reported symptoms should be corroborated by an informant familiar with the patient’s premorbid and current condition!

1. GAIT APRAXIA* (90%) – most frequent first symptom: slow, unsteady, wide based gait; “magnetic gait” (short steps + difficulty picking feet off ground); difficult turning (takes several steps)

   Other gait synonyms: “apractic,” “bradykinetic,” “glue-footed,” “parkinsonian,” “short-stepped,” and “shuffling.”

   - legs are bradykinetic (vs. Alzheimer disease – normal gait).
   - disturbed in stance with tendency to lean forward and imbalance exacerbated by eye closure – “hydrocephalic astasia-abasia”
   - normal motor force, tone, and reflexes.
     upper motor neuron signs or lower limb weakness may be indicative of cervical myelopathy and lumbar canal stenosis, respectively!
   - discrepancy between walking and simulated walking (eliminates pyramidal lesion) - can move legs well and imitate walking while in chair, but becomes awkward and severely impaired as soon as attempts to walk.
   - difficulty in handwriting and dressing.
   - differentiation from parkinsonism:
     — Parkinson's patients are able to increase their stride length and walking cadence with aid of external cueing such as counting; vs. patients with NPH have gait apraxia that does not respond to such aids.
     — patients with NPH mobilize with relatively preserved arm swing.

Criteria to classify gait as “probable NPH” - at least two of the following should be present and not be entirely attributable to other conditions:

   a. Decreased step height
   b. Decreased step length
   c. Decreased cadence (speed of walking)
   d. Increased trunk sway during walking
   e. Widened standing base
   f. Toes turned outward on walking
   g. Retropulsion (spontaneous or provoked)
   h. En bloc turning (turning requiring three or more steps for 180 degrees)
   i. Impaired walking balance, as evidenced by two or more corrections out of eight steps on tandem gait testing

2. COGNITIVE IMPAIRMENT (mild ÷ moderate) – subcortical frontal dysexecutive syndrome: reduced attention, memory loss, difficulty planning, slowness in thought, apathy.

   - aphasia is uncommon.
   - headache is uncommon (look for other causes of it).
   - pathophysiologic mechanism - compromised microcirculation, due to increased intraparenchymal pressure (PET shows widespread glucose utilization defects in subcortical and cortical regions).

Criteria to classify cognition as “probable NPH” - at least two of the following should be present and not be entirely attributable to other conditions:
a. Psychomotor slowing (increased response latency)
b. Decreased fine motor speed
c. Decreased fine motor accuracy
d. Difficulty dividing or maintaining attention
e. Impaired recall, especially for recent events
f. Executive dysfunction, such as impairment in multistep procedures, working memory, formulation of abstractions/similarities, insight
g. Behavioral or personality changes

3. **Urinary Incontinence**

Criteria to classify urinary continence domain as “probable NPH” – either one of the following should be present and not be entirely attributable to other conditions:

a. Episodic or persistent urinary incontinence
b. Urinary and fecal incontinence

Or any two of the following should be present:

a. Urinary urgency as defined by frequent perception of a pressing need to void
b. Urinary frequency as defined by more than six voiding episodes in an average 12-hour period despite normal fluid intake
c. Nocturia as defined by the need to urinate more than two times in an average night

*relate to stretched fibers innervating legs and sphincters that project through vicinity of frontal horns of ventricular system;

| early hypothesis suggested that enlargement of the ventricles led to compression and/or deformation of the upper motor neuron fibers passing through the medial portion of the corona radiata. |
| EMG evidence reveals contraction of antagonistic muscle groups and abnormally increased activity in the antigravity muscles acting on hip and knee joints - gait disorder of INPH is a disturbance in the phased activation of muscle groups (disorder of subcortical motor control) rather than a primary pyramidal disturbance. |

In addition, other symptoms have been reported: lethargy, apathy, impaired wakefulness, visuospatial disturbances.

### Clinical Course

- insidious onset (versus acute)
- origin after age 40 yr
- minimum duration of > 3-6 mo
- progression over time

### Diagnosis – Routine Tests

**CT / MRI**

- hydrocephalus with little or no cortical atrophy (vs. Alzheimer disease) + no evidence of obstruction to CSF flow (look for flow voids on MRI in aqueduct)

  maximal width of *frontal horns* measure > 30% of maximal biparietal diameter (i.e. Evans’ index > 0.3)
ventricular inferior horns are > 2 mm (not entirely attributable to hippocampus atrophy)

- although not common, **transependymal CSF flow** occasionally can be seen.
- diameter of the corpus callosum decreases in many cases as the dorsal surface of the ventricle domes upward

A. T1-MRI - dilatation of lateral ventricle, stretching of corpus callosum (arrows), depression of 3rd ventricle floor (single arrowhead), enlargement of aqueduct (double arrowheads).

B. T2-MRI - dilatation of lateral ventricles.

Ventriculomegaly, periventricular lucency (inferior arrow), and white matter hyperintensities (superior arrow):
**Callosal Angle**

NPH stretches lateral ventricles superiorly – grows Mickey Mouse ears

- proposed as a useful marker of idiopathic NPH in distinguishing from those with *ex-vacuo ventriculomegaly*.
- angle should be measured on a coronal image perpendicular to the AC-PC plane at the level of the posterior commissure.
- patients with NPH have smaller angles than those with ventriculomegaly from atrophy or normal controls.
  - normal angle is 100-120°
  - in NPH angle is 50-80°
  - in one study, symptomatic NPH patients who responded to shunting had a significantly smaller mean preoperative callosal angle (59°, 95% CI 56-63°) compared with those who did not respond (68°, 95% CI 61-75°).

**Sulcal Morphometry**


“NPH stretches lateral ventricles superiorly so superior sulci get compacted vs. inferior sulci stretched”

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**NPH group vs vascular cognitive disorder group:**
calcarine/cingulate ratio $\geq 0.96$ had an excellent sensitivity (96.8%, 30/31) and a good specificity (80.0%, 28/35) whereas a lateral/intraparietal ratio $\geq 1.49$ had a fair sensitivity (77.4%, 24/31) and an excellent specificity (97.1%, 34/35).

NPH group vs healthy controls group:

- the best parameter to differentiate NPH patients from healthy controls was the calcarine/cingulate ratio (AUC = 0.96; 95% CI = 0.91, 1.00); cut-off value $\geq 0.95$ had a sensitivity of 96.0% (24/25) and a specificity of 88.0% (22/25).

Conclusion - the best parameter to discriminate shunt-responsive NPH from vascular cognitive disorder and healthy controls was the ratio between calcarine sulcus and cingulate sulcus opening with an area under the curve of 0.94 (95% CI: 0.89, 0.99); cut-off value of 0.95 provided the highest sensitivity (96.8%) and specificity (83.3%).
• diagnosis of NPH is complicated by the variability in its clinical presentation and course.
• these test are not required routinely but may increase confidence in the diagnosis in selected cases.

**ICP MONITORING**
- intermittent pressure B-waves (decreased brain compliance), particularly during REM sleep; slowly increase ventricular size and lead to ischemic damage.

**SPECT-ACETAZOLAMIDE CHALLENGE**
- decreased periventricular perfusion that is not altered by acetazolamide.

Historical tests:
**Radioisotope cisternography** (not particularly specific) - isotope injected intrathecially:
• normal - isotope is seen around brain convexity within 48 hours;
• NPH - isotope reflux into ventricles and stasis beyond 48 hours; delayed clearance of radiotracer over the cerebral convexities after 48–72 h

**CSF DYNAMIC TESTS**
Three supplementary tests:
Current guidelines recommend that all patients suspected of having idiopathic NPH be considered for supplementary tests with one or more of the three methods

1. **Lumbar puncture “tap test”** – high-normal CSF pressure (6-24 cmH₂O), normal CSF composition.
   - **Removal of 40-50 ml CSF → transient clinical improvement in cognitive & gait dysfunction!***
   - *73-100% positive predictive value to indicate better prognosis with shunting; but low sensitivity (26-61%).
   • left lateral decubitus position
   • zero point of the manometer is being positioned at the approximate height of the atrium of the heart.
   • before a pressure reading is made, the patient should be fully relaxed, preferably with the legs extended, for a period of 5 minutes after the spinal needle is introduced.
   • pulsation of the CSF column should be visible in synchrony with the heartbeat to ensure that the end of the needle is in good continuity with the subarachnoid space at the time of measurement.

2. **Measures of CSF outflow resistance** - thought to reflect CSF absorption pathways.
   • fluid is injected into CSF space (e.g. ventricles or lumbar sac) either by bolus or infusion.
   • CSF outflow resistance can then be calculated with pressure-volume study and used to assess CSF circulation for signs of disturbance.
   • In Dutch NPH study, outflow resistance > 18 mm Hg/mL/min had specificity of 87% and sensitivity of 46%.
   • can also be performed through preimplanted ventricular reservoir device.

3. **Prolonged external lumbar drainage** (in excess of 300 mL, e.g. 3 days at 5 mL/hr) – highest sensitivity (50-100%), specificity (80%), and positive predictive value (80-100%).

**DIFFERENTIAL DIAGNOSIS**
NPH can resemble, or occur in combination with, various disorders that are prevalent in the elderly, such as cerebrovascular disease*, neurodegenerative disorders (e.g., Alzheimer’s, Parkinson’s, Lewy body disease), primary urological disorders, spinal stenosis.

N.B. these coexistences may make patients not to respond to shunt (false-negative response)!

*bilateral multiple lacunar strokes (état lacunaire) can give all three symptoms!!! see p. Vas3 >>

Ventriculomegaly + absence of full triad symptoms = generally not NPH
No any single component of clinical triad = unlikely NPH
No ventricular enlargement even if with some or all of the triad symptoms = unlikely NPH
Papilledema or ICP↑ = unlikely NPH

GAIT DISTURBANCE

Vascular
- Cerebrovascular disease
- Stroke
- Multi-infarct dementia
- Binswanger's disease

Neurodegenerative
- Parkinson's disease
- Alzheimer's disease
- Progressive supranuclear palsy
- Frontotemporal dementia

Miscellaneous
- Peripheral neuropathy
- Cervical myelopathy
- Lumbar canal stenosis
- Diabetic neuropathy
- Autonomic dysregulation
- Spinal neoplasm

DEMENTIA

Vascular
- Cerebrovascular disease
- Stroke
- Multi-infarct dementia
- Binswanger's disease
- CADASIL (cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy)

Neurodegenerative
- Parkinson's disease
- Alzheimer's disease
- Progressive supranuclear palsy
- Frontotemporal dementia
- Corticobasal degeneration
NPH

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**URINARY INCONTINENCE**

*Structural*
- Bladder outflow obstruction
- Benign prostatic hypertrophy

*Bladder innervation*
- Autonomic dysregulation
- Lumbar canal stenosis

*Miscellaneous*
- Medications—anticholinergics, diuretics

**TREATMENT**

- Ataxia, dementia, and incontinence associated with more advance stages (> 2 years’ duration) of NPH tend to be less responsive to treatment. *Early treatment can be instrumental* in achieving an optimal treatment outcome and avoiding irreversible impairments.

1. **ACETAZOLAMIDE** or **DIGOXIN** to decrease CSF production.

2. **VENTRICULAR SHUNTING:** patient selection criteria:
   1) Mild dementia of < 2 years’ duration
   2) Typical gait and urinary dysfunction
   3) Rapid CSF flow in 4th ventricle and cerebral aqueduct (seen as accentuated signal loss on heavily T2-weighted images).
   4) No MRI evidence for multi-infarct state*

   *Deep white matter T2 hyperintensities (marker of comorbidity); some studies showed inverse correlation with shunt responsiveness; other studies found no correlation.

   N.B. Only 60-80% patients experience long-term benefit (gait improves more than memory).

3. Alternative methods of shunting:
   a) **Lumboperitoneal shunting** - significantly greater likelihood of need for shunt revision and greater overall charges to the health care system.
   b) **ETV** - success rates generally reported around 70% (i.e., efficacy similar to that of VPS)
   c) **Lumbar subcutaneous shunt** proposed by Mendelow’s group.
even if patient selection is as good as it could be, the 61.2% rate of improvement with shunting is expected; i.e. there are cases of probable NPH that are “shunt-nonresponsive”

- gait and balance are the most common symptoms to improve after both temporary and permanent CSF diversions, whereas cognition is generally recognized as the least likely symptom to improve in NPH.

- patients can cognitively improve after ventriculoperitoneal shunting; Rey Auditory Verbal Learning Test-L (RAVLT-L) was the only neuropsychological test to demonstrate statistically significant improvement both postlumbar drain and postshunt, i.e. improvement on the RAVLT-L postlumbar drain predicted improvement on the RAVLT-L postshunt!!!


A multivariate logistic regression demonstrated that only RAVLT-L improvement after lumbar CSF drainage could predict post-VPS improvement. No other neuropsychological tests were helpful in determining cognitive improvement either post-LD or post-VPS. Even patients with relatively poor baseline cognition have the ability to improve after VPS as long as they demonstrate improvement post-LD - if the patient improves by approximately 5-10 words on the RAVLT-L portion after lumbar CSF drainage, one can likely expect post-VPS cognitive improvement regardless of other factors.

Interestingly, though the RAVLT appears to be one of the best objective measures of cognitive improvement in NPH patients, it does not correlate with patients’ subjective feelings on cognitive improvement as well as measures of visual memory.

Rey Auditory Verbal Learning Test-Learning (RAVLT-L) scores for NPH patients. A, Mean RAVLT-L raw score significantly improves both post-LD and post-VPS compared to baseline testing. *P = .047, **P = .0031, 1-sided t-test. B, Post-VPS RAVLT-L improvement is correlated with post-LD RAVLT-L improvement in a linear fashion (R2 = 0.43, P = .015). C, RAVLT-L improvement after lumbar CSF drainage (post-LD) follows a right-skewed normal distribution. D, When split into 2 groups based on RAVLT-L improvement (>3 points) post-LD, responders demonstrated a significant difference in RAVLT-L score post-VPS. **P < .0001, 2-sided t-test.
A multivariate logistic regression demonstrated that only RAVLT-L improvement after lumbar CSF drainage could predict post-VPS improvement.

**BIBLIOGRAPHY** see p. S50 >>