Normal Pressure Hydrocephalus

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Disclosures

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  - ONO pharmaceuticals
  - Transposon therapeutics
  - Integrated Research Labs
- No relevant conflicts of interest

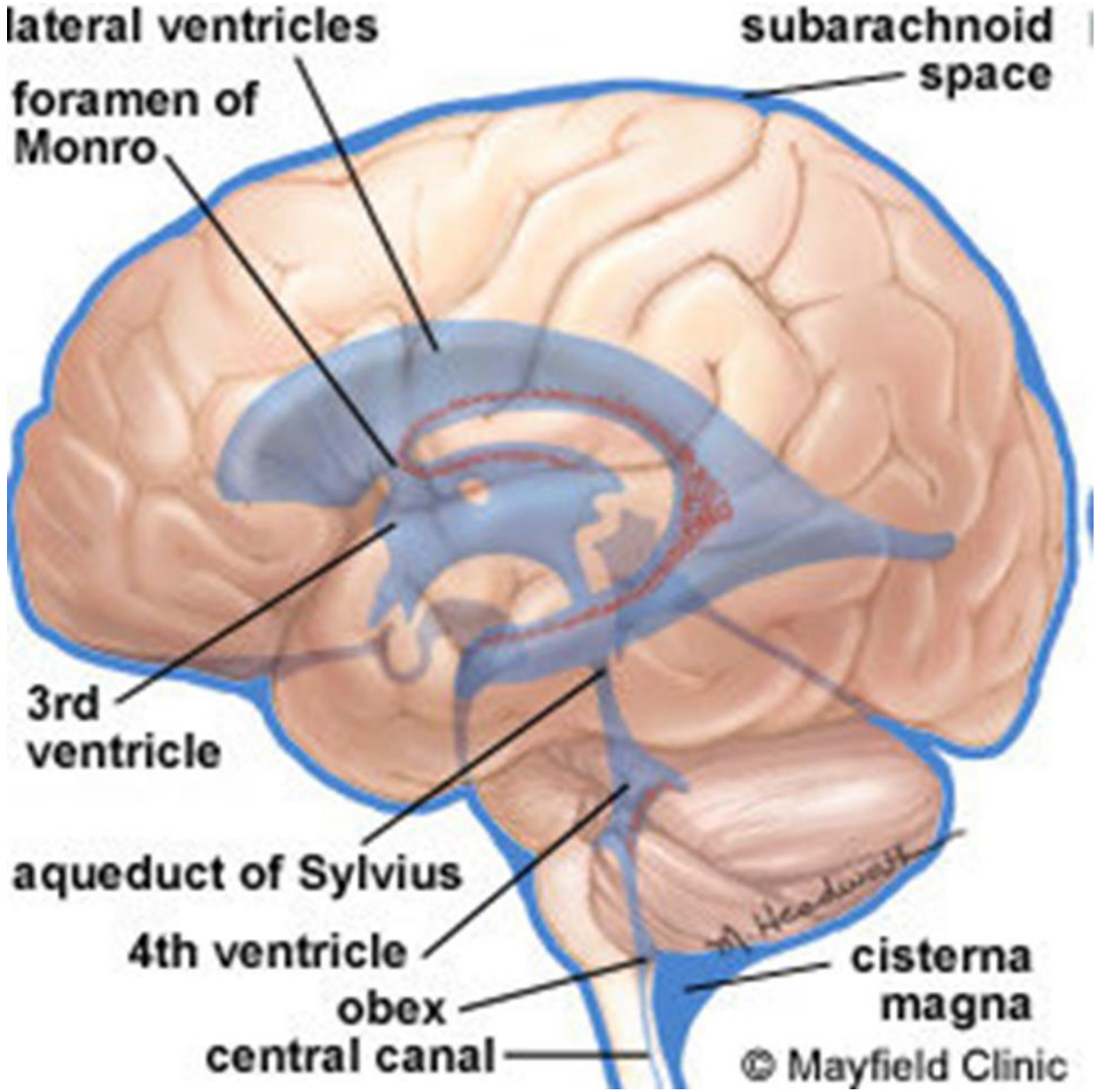
Objectives

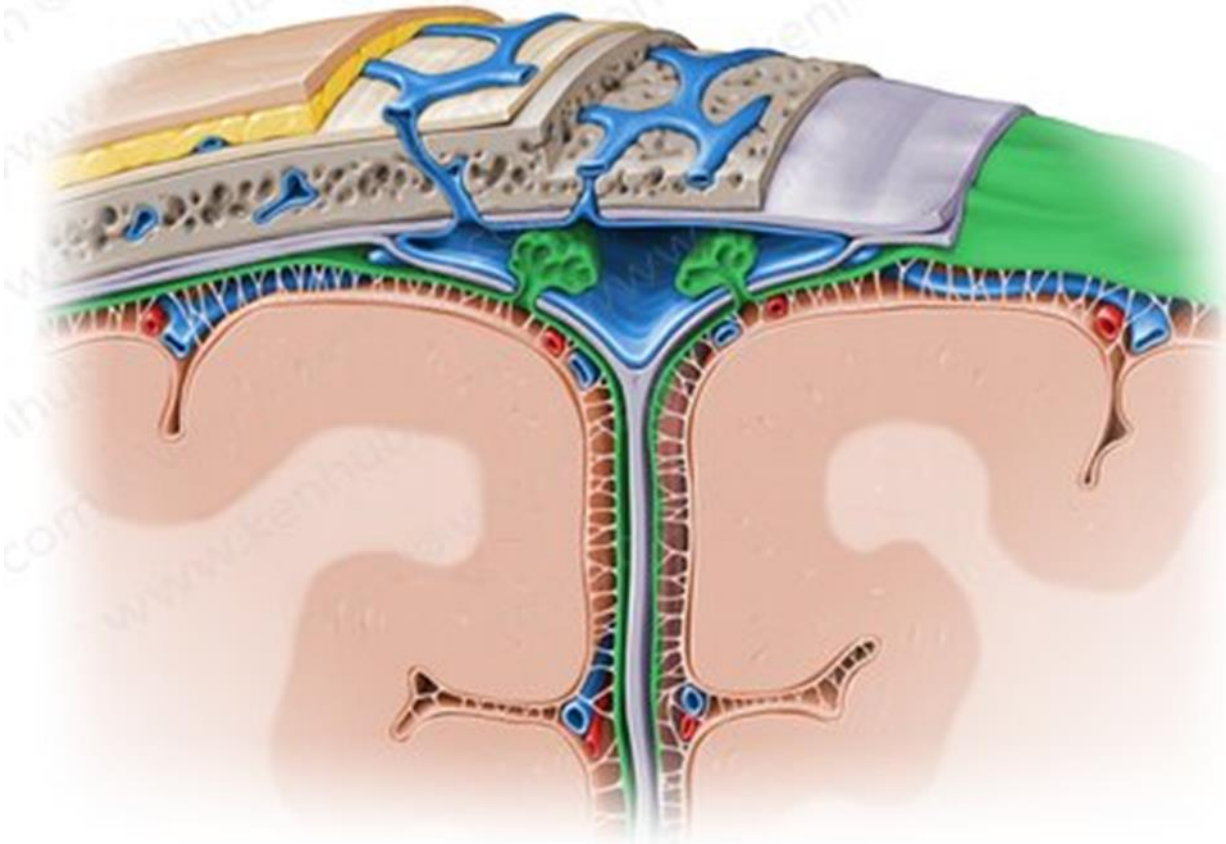
- Review clinical and imaging findings suggestive of NPH
- Present updates on disease models and theories of NPH pathophysiology
- Discuss the limitations of current clinical science of NPH, regarding diagnosis, treatment, and pathophysiology
- Review workup and treatment protocols from our NPH program

74 yo woman
Lost balance turning in kitchen 3 yrs ago
Gait progressively worse since: shuffle, walker, wheelchair, repeated falls, magnetic
Difficulty with balancing checkbook and planning
Urinary incontinence past 6 months “unwitting wetting”
Manual function normal
Speech and swallow normal

PMHx and FHx clear

On exam no tremor
Voice normal
Alternating motions hands normal, legs borderline
Tone paratonic in legs only
Gait magnetic


lateral ventricles
foramen of Monro
subarachnoid space
3rd ventricle
aqueduct of Sylvius
4th ventricle
obex
central canal
cisterna magna
© Mayfield Clinic



Theory of NPH etiologies and pathophysiology

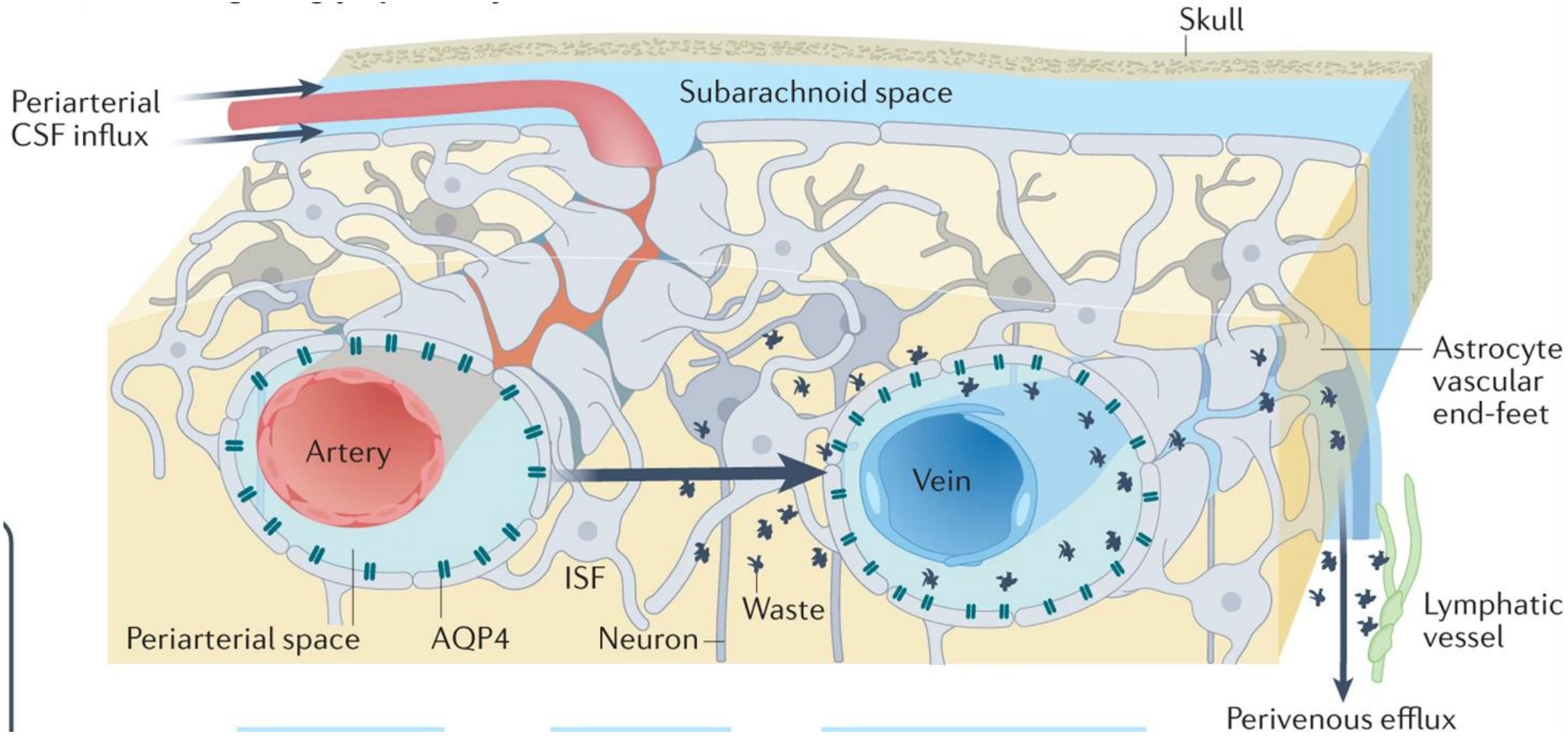
Increased resistance to CSF outflow

- ? old subclinical meningitis
- ? old subclinical subarachnoid hemorrhage
- ? old head injuries
- ? old age

- -> CSF retention
- -> raised pressure in sulci and ventricles [temporary or episodic?]
- -> ventricular enlargement and DESH

- Mechanical stress: periventricular axons more impacted
- Vulnerability to water hammer injury from cardiac pulse pressure
- Impaired glymphatic irrigation, retention of metabolites, neurodegeneration

“Glymphatic” circulation



A brief history of NPH

- “The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure” Hakim and Adams 1965
  - Clinical triad of gait apraxia, urinary incontinence and cognitive decline
  - Imaging evidence of hydrocephalus
  - Disability reversed with shunt
- Few histology reports
- Evolving shunt technology
- Limited evidence that shunt helps NPH
  - Series of surgical case reports of variable quality
  - One DB-RCT of shunt for NPH reported (2011). Was positive, n = 14
  - One open-label RCT reported (2015). Also positive, n = 93
  - AAN practice guidelines class C evidence for shunt, need additional RCTs (2015)
- Over-diagnosed; threshold for shunting somewhat arbitrary
- All/part neurodegeneration? neuronal loss amyloid/tau aggregation common
- Is NPH real? Radical non-believers, radical believers, and everything in between
- Movement Disorder panel expressed skepticism, called for higher quality evidence

NPH by the numbers

- Prevalence at age 70 estimated 1% of women 2% of men
- Incidence 5.5 new diagnosis per 100,000 population per year
- Approx 1000/yr new shunts in USA for NPH
- Average age of diagnosis mid 70s
- Response to shunt commonly cited at 70-80%
- Rate of intracerebral bleed or fluid collection 10%+
- Rate of hardware infection 2%
- Rate of shunt failure 10-30% in first year

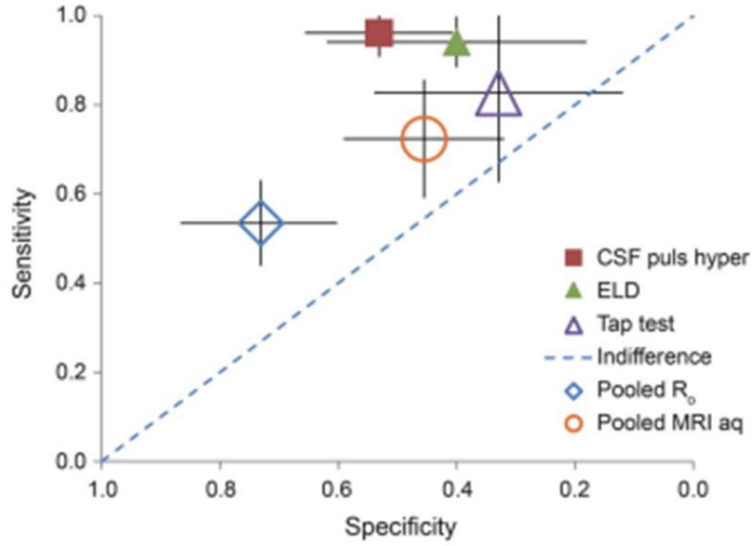
The problem with diagnosing NPH

- After age 70
  - Gait, cognitive, bladder symptoms are common
  - Ventricular enlargement on imaging is common
  - Dual or multiple cerebral pathologies are common
- Diagnosis of NPH is only “confirmed” by response to shunt
  - What is a “response”?
  - How about someone not operated?
  - If there is poor outcome due to surgical complication, was it NPH?
  - What is meant by “NPH too advanced” as explanation for non-response
- When NPH is called, the patient is typically shunted
  - Natural history untreated is not clear
  - Is some of “response” a placebo effect? regression toward mean?
- No gold standard test
  - Claims for tests to have high predictive value are not credible

Tests that are somewhat predictive of shunt response (There are not really diagnostic tests for NPH)

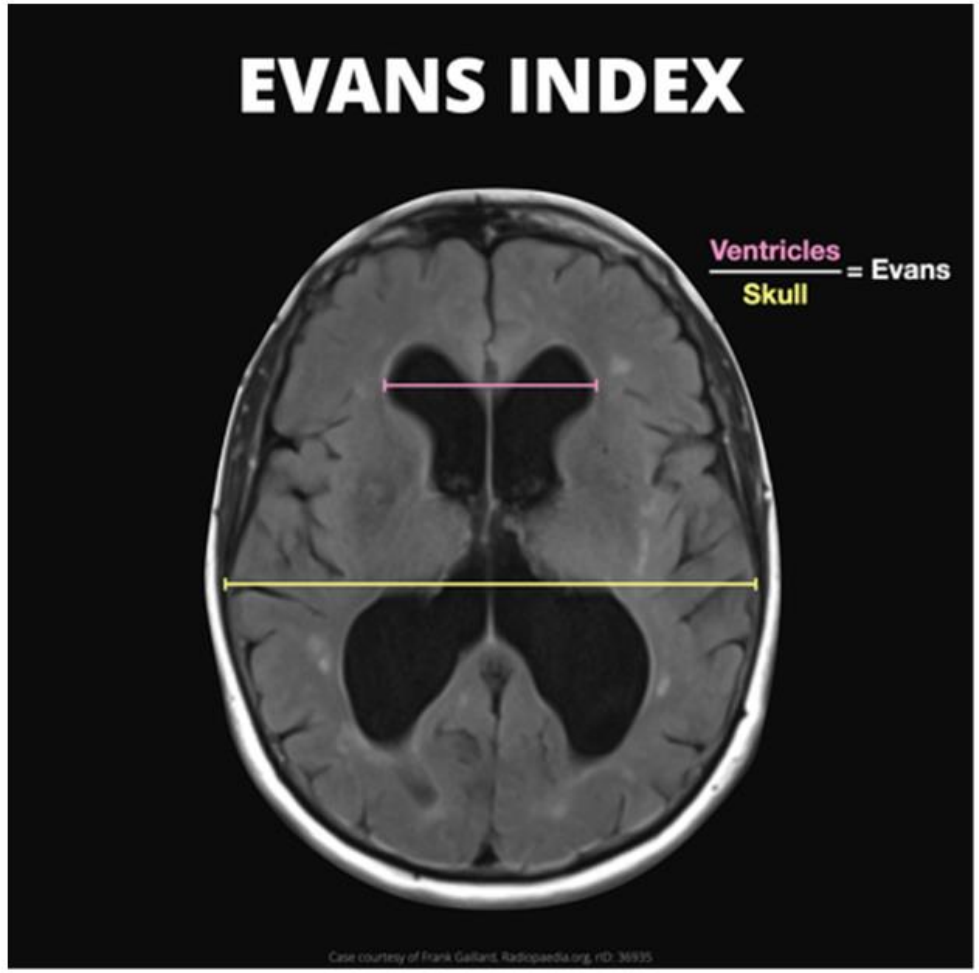
- CT/MRI
  - Evan's Index > 0.3
  - DESH
  - ~~Increased aqueductal flow~~
- ~~Intrathecal radionuclide~~
  - ~~Scintigraphy or cisternography~~
- Large vol tap or Lumbar drain trial
- CSF pressure profile and lumbar infusion test

Figure 2 **Receiver operating characteristic curve showing the incremental benefit of each of the discussed modalities**



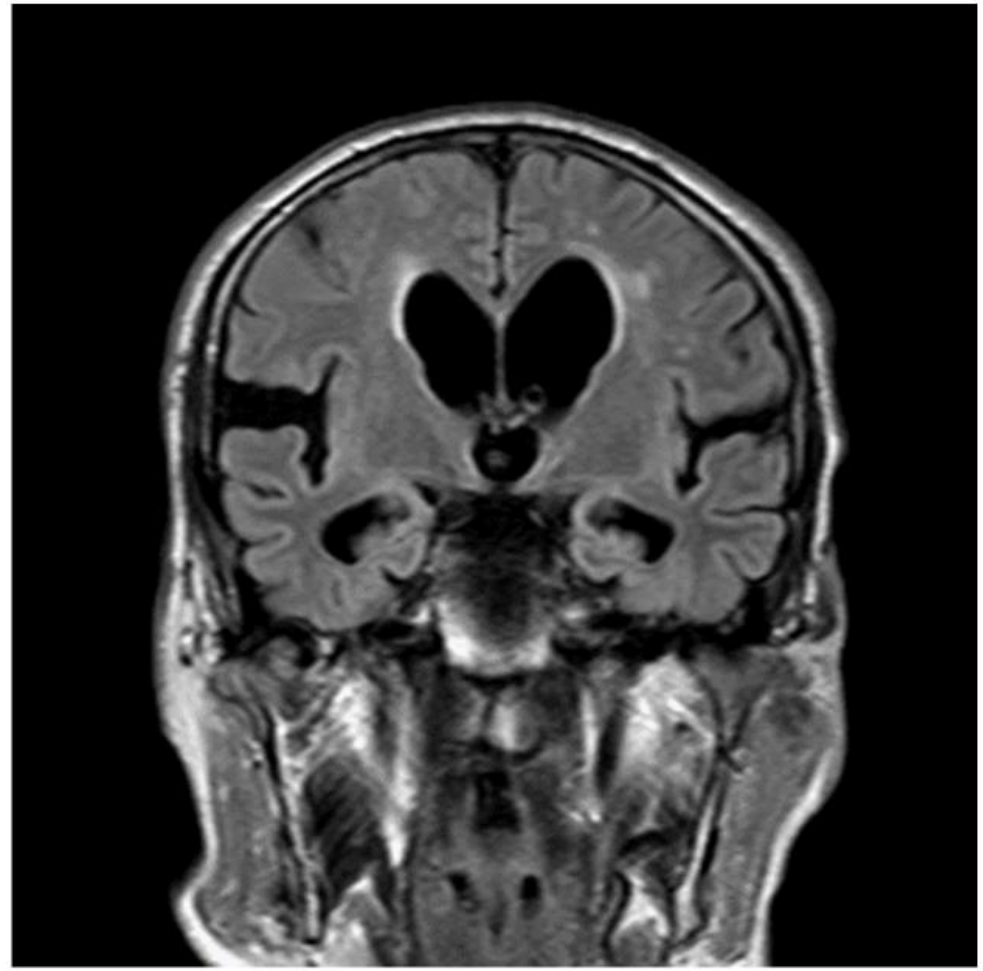
Measure of relative sensitivity and specificity of the different techniques described; studies are as listed in figure 1. Increased CSF pressure elevations in response to arterial pulsations[16] are labeled CSF puls hyper. Results from studies in columns 4,[18] 5,[19] 6,[20] and 11[17] of figure 1 were combined to provide a pooled assessment of R_o. Results from studies in columns 7,[26] 8,[28] and 9[27] were combined to provide a pooled assessment of elevated CSF flow by MRI. Results from studies in columns 2[31] and 10[17] were combined to provide a pooled assessment of the CSF tap test. ELD – external lumbar drainage.

Ventricle enlargement



20% of population > 70 yrs have EI > 0.3

DESH: Tight high conv + wide sulci

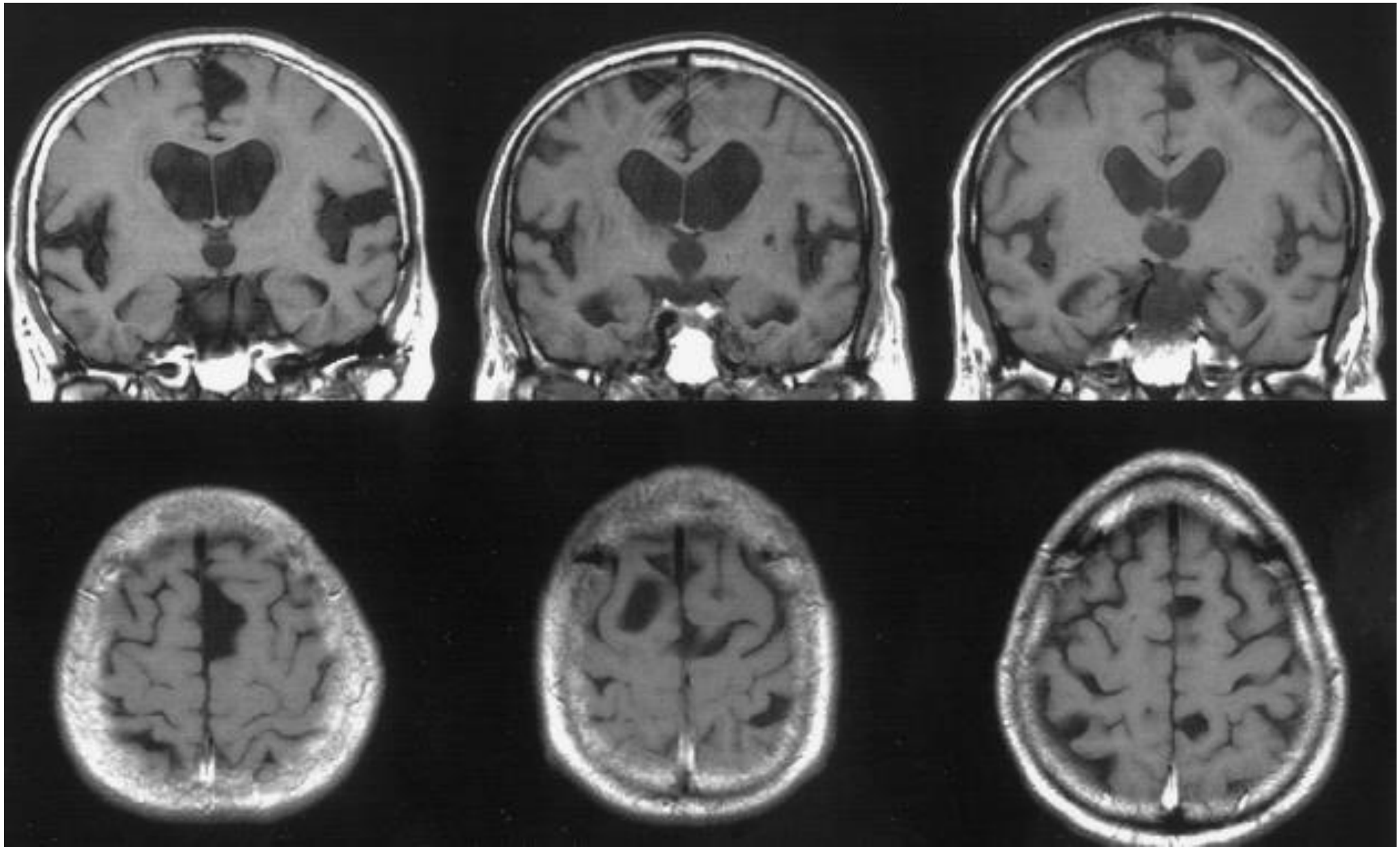


5% of population > 70 yrs have EI > 0.3 plus DESH

Sylvian enlargement++, trapped sulci

Sylvian+, trapped sulci

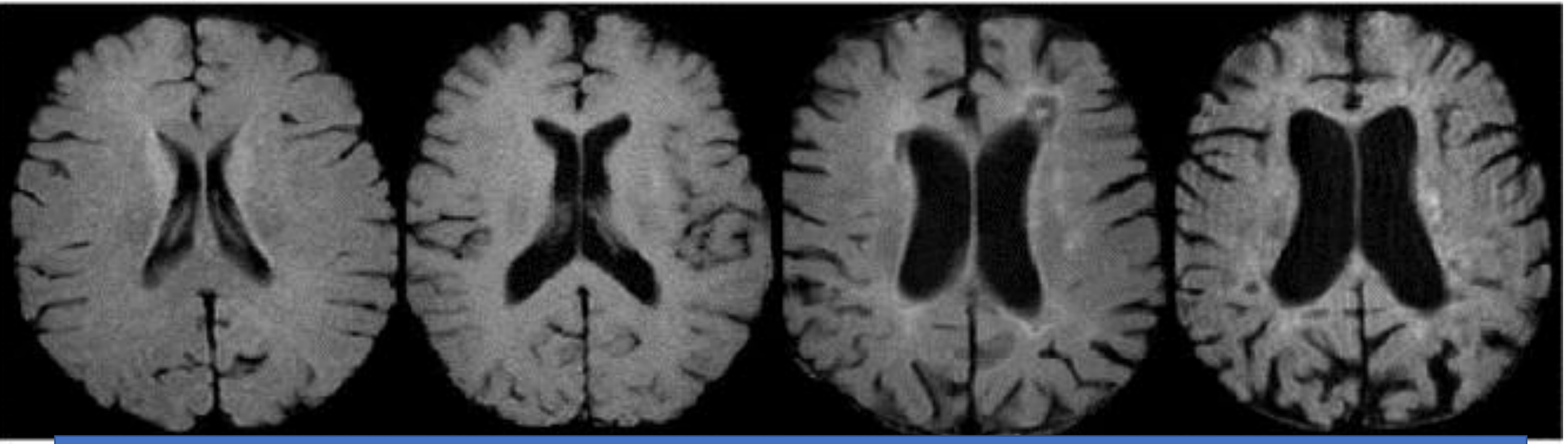
Sylvian+/- sulci +/-



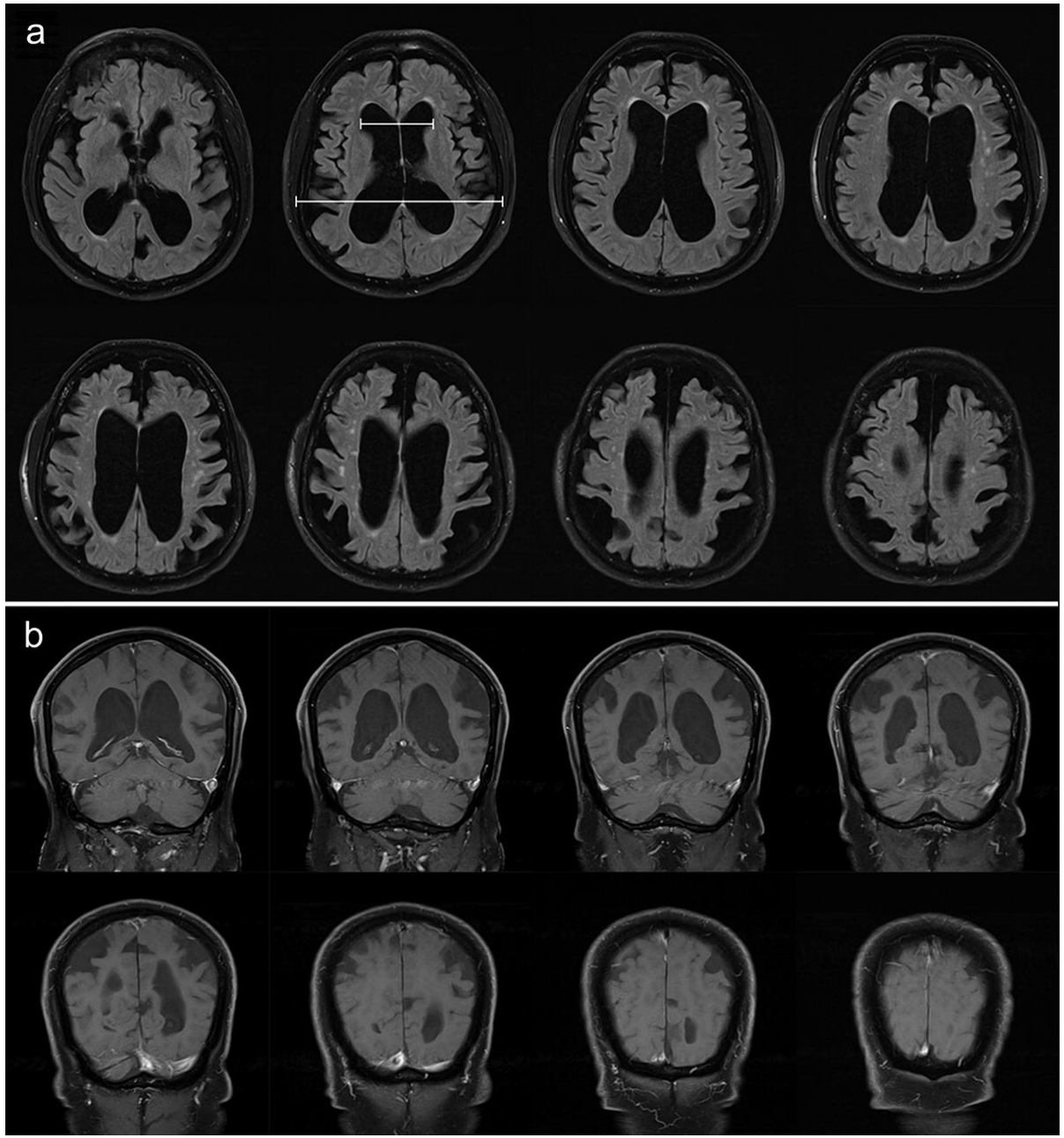
Main differential of NPH is cerebral degeneration

eg Alzheimer, frontal degeneration, PSP, HD, etc etc

Below is a case of progressive cerebral degeneration, not NPH



Case of NPH with disproportionately enlarged subarachnoid space (DESH) misdiagnosed as cerebral degeneration



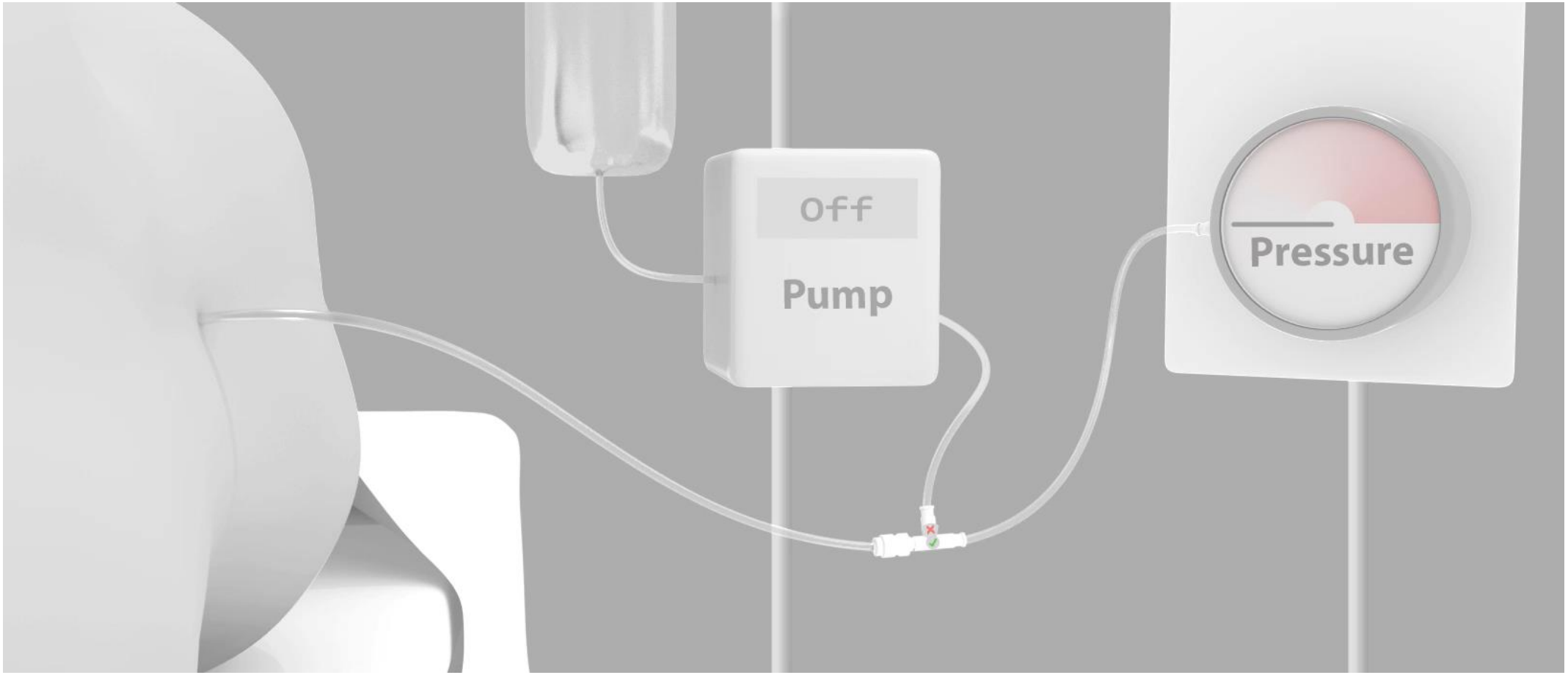
McCarty, Neurocase 2018

Lumbar drain trial

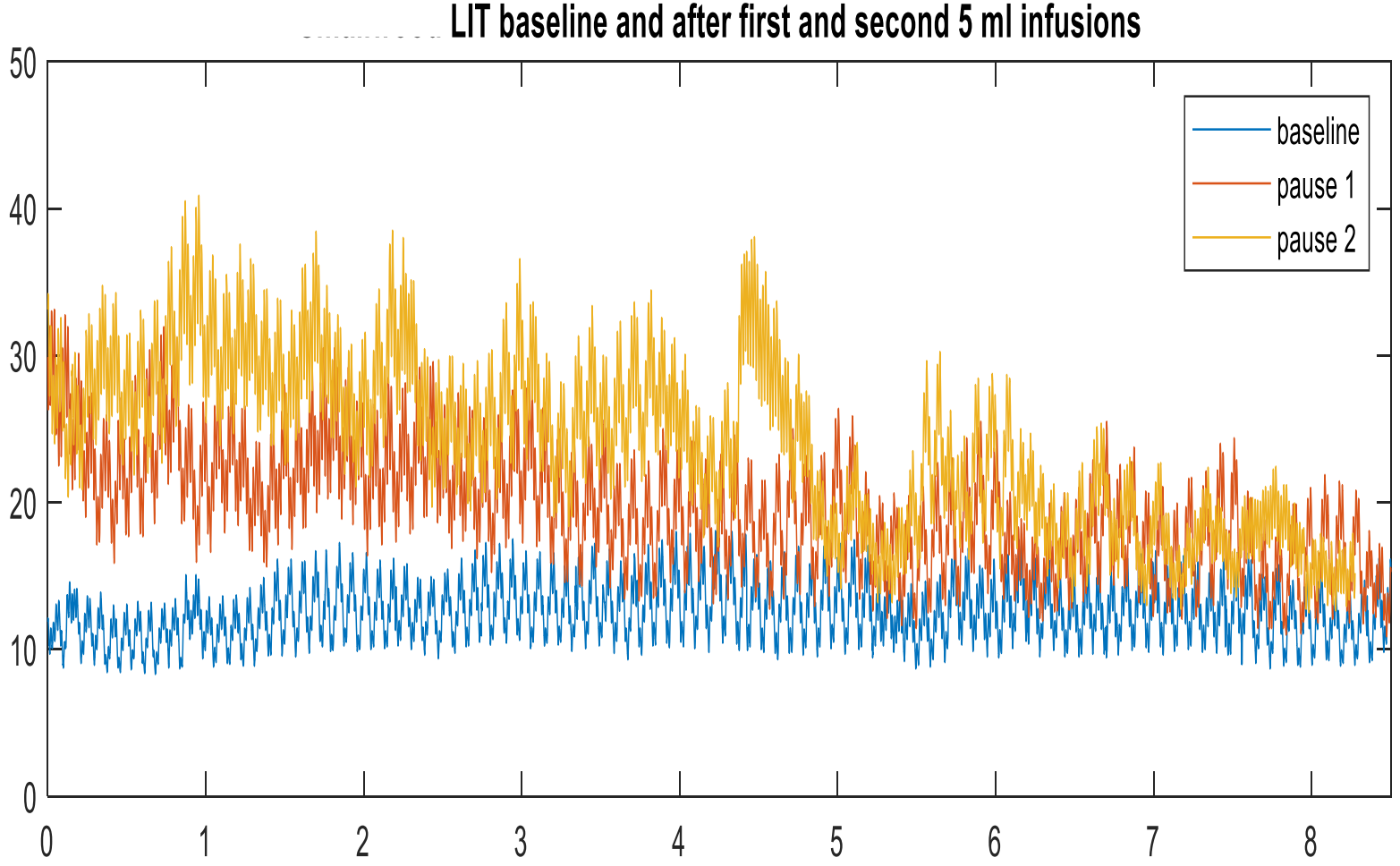
- Baseline assessment
  - Trails B
  - 10 M walk time, steps, miniBEST
- Lumbar catheter inserted and connected to drainage bag
- Every 4 hours, 20 mls CSF drained, till total 300 mls removed
- Post-drainage assessment
  - Trails B
  - 10 M walk time, steps, miniBEST
- A 10% improvement in one or more outcomes is seen as supportive

- Caveats
  - how much to drain, when to test, how much change is meaningful?
  - false positive and false negative
  - might shunt do secondary prevention rather than reversal

Lumbar infusion test



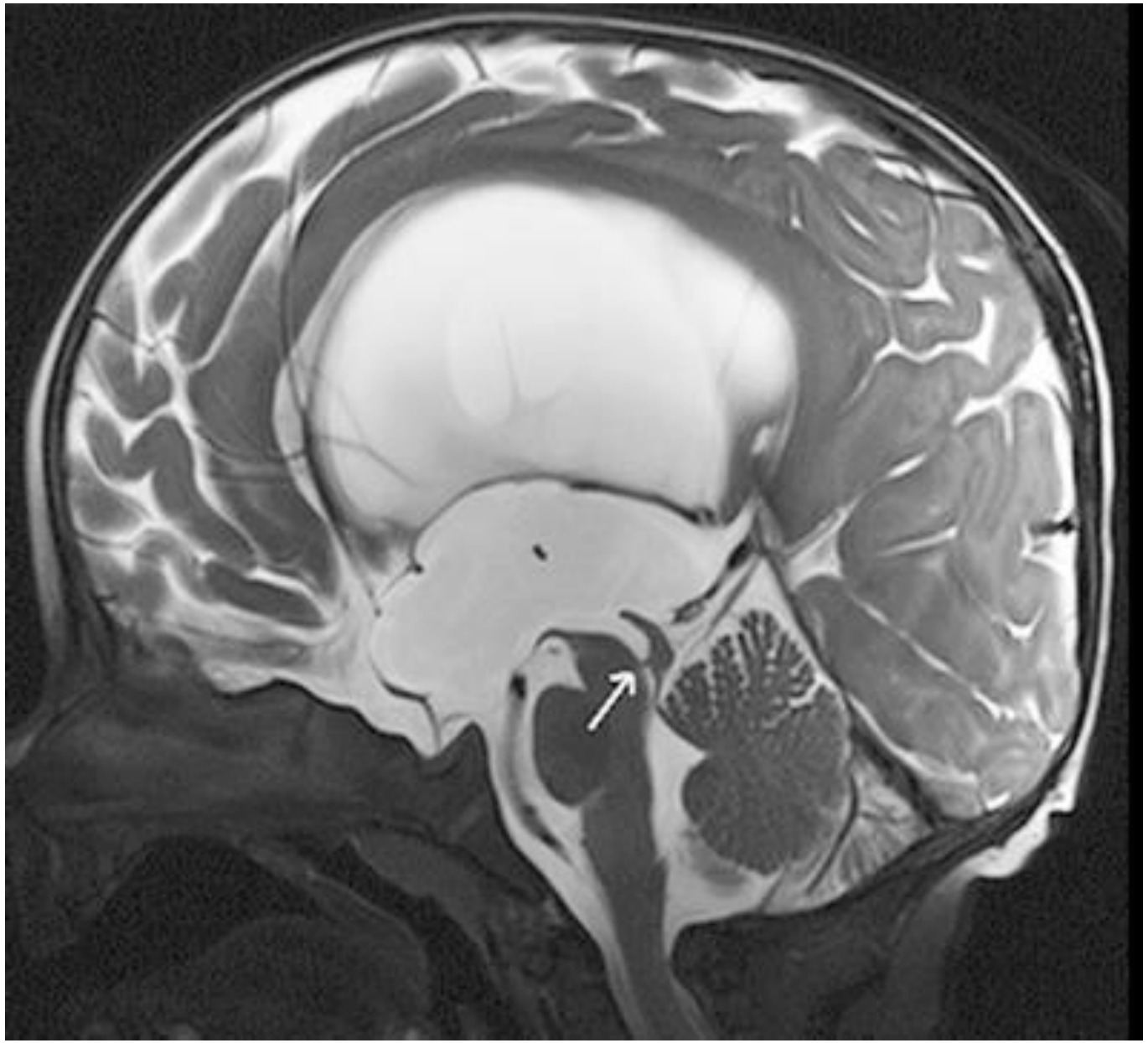
CSF pressure 8 mins baseline and after infusions



Differential diagnosis:

Late onset ventriculomegaly with aqueductal web

Macrocephaly suggests late adult symptom-onset of congenital stenosis can occur



Are some cases of NPH due to loss of CSF propulsion?

- There are families with NPH
  - WGS and linkage suggests mutations in genes related to cilia

- Video of CSF propulsion in zebrafish:
  wild type, then 3 diff mutations of cilia motility

- https://ars.els-cdn.com/content/image/1-s2.0-S0960982218315896-mmc6.mp4

NPH program at UT Southwestern

- Protocols for evaluation and management
  - Interdisciplinary clinic
    - Neurology assess H+P
    - Neuropsychological assessment of profile and severity of cognitive impairments
    - PT measure gait-balance features
    - Neurosurgery assess surgical risks
  - Diagnostic-prognostic testing, seeking preponderance of evidence
    - Quantitative MRI incl sulci, volumes
    - CSF pressure profile incl B waves and pulsation pressure
    - Lumbar infusion test 30 mls saline infused over 20 mins
    - Lumbar drain 20 mls/hr every 4 hours for 2.5 days = 300 mls: gait and cognition pre-post
- Registry for quality control and research
  - Standardized outcome measures baseline and annual thereafter
  - mRS, NPH score, PROs, Trails A&B and RBANS, miniBEST, 10m walk, 360 turn
  - Complication rates

Non-surgical management

- Physical therapy
- Environmental adaptations eg gait aids
- Manage BP: preference for ARB and Ca Channel blockers
- Healthy sleep and exercise patterns
- Solifenacin or vibegron for bladder
- Cognitive rehab?
- Cholinesterase inhibitors for memory?