Neuroimaging approaches for elucidating disease mechanisms in hydrocephalus

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An analogy: Clinico-radiological paradox

Don’t treat the scan!
Three-day CSF drainage barely reduces ventricular size in normal pressure hydrocephalus.


RESULTS:

- Drain volume was 415 mL (median 470 mL, range 160-510 mL). Ventricular size was reduced in all patients, averaging 3.7 mL (SD 2.2 mL, p < 0.001), which corresponded to a 4.2% contraction. **The ratio of volume contraction to drain volume was only 0.9%.** Seven patients improved in gait and 6 in attention. Ventricular reduction and total drain volume correlated neither with improvement nor with each other. The 7 patients with the largest drain volumes (close to 500 mL), had ventricular changes varying from 1.3 to 7.5 mL.

CONCLUSIONS:

- **Clinical improvement occurs in patients with NPH after ELD despite unaltered ventricles, suggesting that ventricular size is of little relevance for postshunt improvement or determining shunt function.** The clinical effect provided by ELD, mimicking shunting, is probably related to the recurring CSF extractions rather than to the cumulative effect of the drainage on ventricular volume.
Advanced imaging techniques

→ insight into function
and structure/function relationships

• CSF flow
• Compliance
• Blood flow
• White matter integrity
• Metabolism
• Brain function/connectivity
**CSF flow**

- **Techniques**
  - Cine phase contrast MRI
  - Quantitative measures
    - SV, flow rate, peak velocity, …
    - wide variability, technique/machine dependent !!

- **Mechanisms**
  - “Redistribution”
    - Increased brain pulsatility
    - Capillary pulsatility (pulse wave encephalopathy – ala Greitz)
  - Intracranial compliance
CSF flow – general findings

**Diagnosis**

- Luetmer (Neurosurgery 2002)
  
  18 ml/min (flow rate)
  
  \[ FR \sim SV \times 2 \times HR \rightarrow 130 \, \mu l \]

**Prognosis**

- Bradley (1996) - 42 \, \mu l


There is abundant literature on the association of pulse pressure and coronary disease.

But is it causative?

Pulsatility Redistribution Hypothesis

**NORMAL**
- Reduced Shear Forces
- Intact Blood-Brain Barrier
- Functional Endothelial Transport

**EXTRA-VENTRICULAR OBSTRUCTION HYDROCEPHALUS**
- Increased Shear Forces
- Altered Blood-Brain Barrier
- Dys-functional Endothelial Transport
Toward mechanisms – Relationship between micro- and macro-pulsations
Is there a relationship between ASV and compliance (by infusion test)?

Miyati et al, Eur Radiol 2003
Changes in aqueductal SV after adjusting for volumetric ventricular volume?

10 patients (mostly NPH)
10 controls

Chiang et al, Invest Radiol 2009
Possible confounds – ASV changes over time (in untreated patients)

Fig 4. Changes in SV values (Table 1) standardized for the estimated onset of NPH, as per the reported first symptoms of NPH.
Possible confounds –
Physiological variation in compliance
Majority of literature to date has been in NPH/adults → data are needed in pediatric HC
4D phase contrast imaging - but what does it mean?
Complex CSF flow patterns by Time-SLIP method

Yamada et al, Radiology 2008
Real-time CSF flow during physiological manipulation (Valsalva)

- Real time Flow
- Beat-to-beat SV
- Heart rate
- Resp. signal

Graphs showing waveforms over time.
Intracranial Compliance

- **Techniques**
  - Invasive techniques (e.g. infusion test)
  - Vascular/CSF flow (Alperin)
  - MR Elastography

- **Mechanisms**
  - ICP
  - Venous stenosis/hypertension
  - Gliosis
  - Pulsatility
How is Compliance Measured Invasively?

- Marmarou et. al. J. Neurosurg, 1975

Apparent Compliance = \( \frac{\Delta V}{(P_p - P_o)} \)

\( \Delta V \) in the order of several mL is used to overcome pressure pulsation.

MRICP is the noninvasive analogous of the volume-pressure response method, except that it does not interfere with the craniospinal hydrodynamics. MRICP measures the naturally occurring \( dV \) and \( dP \) with each heart beat.

Credit: Noam Alperin, U. of Miami
ICP Measurement by MRI: MR-ICP

• MR-ICP is a non-empirical measure based on first principles of craniospinal physiology, and fluid dynamics.
• It utilizes MR velocity imaging of the pulsatile blood and CSF flows to and from the brain.
• It does not require an injection of a contrast.
• MR-ICP scan (< 4 minutes) is used as an add-on for a diagnostic brain MRI exam.

Related References:

Credit: Noam Alperin, U. of Miami
ICP is a mono-exponential function of intracranial volume.

- At low ICP, a small change in volume (dV) causes a small change in pressure (dP).
- At high ICP, the same small volume change (dV) causes a larger pressure change (dP).
- The ratio dV/dP (compliance) is inversely related to ICP.

MRICP measures dV and dP, to derive intracranial compliance and pressure from imaging of the blood and CSF flows to and from the cranial vault.

Credit: Noam Alperin, U. of Miami
The systolic increase in intracranial volume (dV) is derived from the momentary difference between volumes of blood, and CSF that enter and leave the cranium during the cardiac cycle, i.e., arterial inflow (red), venous outflow (purple), and cranio-spinal CSF flow (yellow).
How is dP Measured?

- The pressure change (dP) during the cardiac cycle is derived from the \textit{CSF pressure gradient} (\nabla p), i.e., the pressure difference that causes the CSF to flow out from and back into the cranium.\(^3\)

- The Navier-Stokes equation is used to calculate CSF pressure gradient waveforms from the \textit{CSF velocities}.

\[
\rho \left( \frac{d\mathbf{v}}{dt} + \mathbf{v} \cdot \nabla \mathbf{v} \right) - \mu \nabla^2 \mathbf{v} = -\nabla p
\]

\[\text{inertial force}\]
\[\text{viscous losses}\]


Credit: Noam Alperin, U. of Miami
Intracranial compliance is decreased in NPH
MR Elastography

Freimann et al, Neuroradiology 2012
Compliance is *increased* in NPH
... but no change in compliance with shunting (3 mo)

→ Reconstitution of the micro-mechanical structure of the brain

Freimann et al, Neuroradiology 2012
Is there a difference between global (ICP-mediated) and local compliance?
CBF

- Techniques
  - $^{133}$Xe-CT
  - $^{15}$O PET
  - SPECT ($^{99}$Tc/IMP)
  - ASL MRI (still under “development”??)

- Mechanisms
  - ICP
  - Vascular compression
  - Impaired metabolism
  - Cardiac effects (??)
  - Cause vs. effect still unknown
**CBF – General findings**

- Global CBF reduced pre-shunt (mostly NPH)
- Regions: mostly frontal & anterior temporal
- Periventricular reduction
- Not related to clinical function (correlations in limited # studies)
- Post-shunt – increased
  - related to outcome?

Momjian *et al*, Brain 2004
CBF by PET (NPH)
CBF decreased, global and local (PVWM and GM)

Note poor correlation between CBF and ICP
→ weakens ventricular compression hypothesis

Ower et al, JCBFM 2004
CBF by PET (NPH)
CBF decreased locally (mesial frontal and anterior temporal)
→ correlates with functional impairment
CBF by PCMRI

- Increased with shunting (infants)
- Correlates with changes in ICP and CPP
CBF by ASL (NPH)
Decreased CBF (indep. of outcome)
CBF by SPECT
CBF marginally changed with shunting
→ no difference between responders and non-responders on pre-shunt CBF

**TABLE 5: Preoperative CBF and CVR values in responders and nonresponders**

<table>
<thead>
<tr>
<th>Group</th>
<th>CBF (ml/100 g/min)</th>
<th>No. of Patients</th>
<th>CVR (%)</th>
<th>No. of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>responder</td>
<td>38.2 ± 4.3</td>
<td>146</td>
<td>6.6 ± 6.6†</td>
<td>141</td>
</tr>
<tr>
<td>nonresponder</td>
<td>38.5 ± 6.9</td>
<td>16</td>
<td>12.2 ± 3.2</td>
<td>15</td>
</tr>
</tbody>
</table>

* Five of the 146 responders and 1 of the 16 nonresponders did not undergo CVR measurement.
† p < 0.0025 compared with healthy controls, and p < 0.005 compared with nonresponders.

**TABLE 8: Changes in CBF and CVR values after CSF shunting in responders with the complete or incomplete triad**

<table>
<thead>
<tr>
<th>Shunt Placement</th>
<th>CBF (ml/100 g/min)</th>
<th>No. of Patients</th>
<th>CVR (%)</th>
<th>No. of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>before</td>
<td>37.9 ± 4.4</td>
<td>68</td>
<td>5.1 ± 5.1</td>
<td>62</td>
</tr>
<tr>
<td>after</td>
<td>39.9 ± 4.3†</td>
<td>68</td>
<td>11.1 ± 6.4‡</td>
<td>62</td>
</tr>
</tbody>
</table>

* Six of the 68 responders did not undergo CVR measurement after shunting.
† p < 0.025 compared with the CBF value before shunting.
‡ p < 0.001 compared with the CVR value before shunting.

Decreased CBF due to transependymal CSF absorption??

Chang et al, JNS 2009
Real-time manipulation –
Significant increase in frontal cortical CBF during CSF removal (30-50 cc)

Shojima et al, Surg Neurology 2004
Diffusion

**Techniques**
- MRI - Diffusion weighted imaging (DWI)
- MRI - Diffusion tensor imaging (DTI)

**Mechanisms**
- Ventricular-related compression/stretching
- Demyelination
- Axonal loss
- Edema/Inflammation
The diffusion ellipse

$\lambda_1 \lambda_2 \lambda_3$ – solutions of the diffusion tensor

Sphere $\rightarrow$ isotropic diffusion (FA = 0)
Cigar $\rightarrow$ anisotropic diffusion (FA = 1)

$\rightarrow$ FA – degree of anisotropy of the diffusion
$\rightarrow$ MD/ADC – magnitude of diffusion (indep. of direction)
Why would diffusion NOT be isotropic?

Figure 1 Isotropic and anisotropic diffusion. (A) Water molecules in the brain are constantly moving (i.e., in Brownian motion). When motion is unconstrained, as in the large fluid-filled spaces deep in the brain (i.e., the ventricles, as illustrated in the MR image on the left), diffusion is isotropic, which means that motion occurs equally and randomly in all directions. (B) When motion is constrained, as in white-matter tracts (illustrated on the right), diffusion is anisotropic, meaning that motion is oriented more in one direction than another (e.g., along the y axis rather than along the x axis).

Increased PVWM diffusion in experimental HC

→ Decreased diffusion due to compression of extracellular space??

Massicotte et al, JNS 2000
First demonstration of DTI changes
Areas of decreased AND increased FA
Additional data available from DTI – demyelination vs. axonal loss
↓ FA increased, ↑MD in iNPH

note non-ventricular regions (SLF and SOFF)

Kanno et al, J Neurology 2011
DTI is not restricted to WM:

\[
\downarrow \text{FA increased, } \uparrow \text{MD in hippocampus (iNPH)}
\]

(No NPH/AD difference in hippocampal atrophy)

Hong et al, AJNR2010
FA/MD in corticospinal tract
Correlated with gait performance
(chronic iNPH)
... and improvement with shunting (DWI in infants)
Decrease in MD (and ICP)
Decrease seen in PVWM and deep/cortical GM
Increased FA in caudate
… improves with shunting

Osuka et al, J Neurosurg 2010
Pediatrics – further challenge – WM development
Metabolism (MR spectroscopy)
Decreased glutamatergic metabolism in kaolin HC

Kondziella et al, Neuroscience 2009
Functional MRI ???
Conclusions

- Numerous advanced techniques available for evaluating *functional* changes in hydrocephalus
- Abundant hypotheses wrt mechanisms
- Experimental model systems needed
  … but how relevant are they to human hydrocephalus
- HC is multi-factorial - multi-modality studies needed
- Standardization is critical (esp. wrt CSF flow)
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