Biomarkers: Applications in Hydrocephalus

David Limbrick, MD, PhD
Assistant Professor
Department of Neurological Surgery
Washington University School of Medicine

Opportunities in Hydrocephalus Research:
Pathways to Better Outcomes
Seattle, WA
July 9, 2012
Disclosures

- No commercial interests
- Research support from the NINDS and NICHD
Overview

- Biomarkers in general
- Application to Hydrocephalus
- Work to date
- Early work with markers post-hemorrhagic hydrocephalus
- Functional outcome as a primary clinical endpoint
Biomarkers: General Overview

- **Biomarker**: “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention.”

- **Clinical Endpoint**: “a characteristic or variable that reflects how a patient feels, functions, or survives.”

- **Surrogate Endpoint**: “a biomarker intended to substitute for a clinical endpoint. …predicts [the treatment effect] based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.”

- Subset of biomarkers
- Few biomarkers achieve SE status

NIH Biomarkers Definitions Working Group
*Clin Pharm Ther* 69:89-95 2001
Biomarkers

**Critical Role in Clinical/Translational Research**
- Biomarkers are the foundation of evidence-based medicine
- Without biomarkers, both research and clinical treatment remain empirical
  - Clinical endpoints are often delayed years or longer
- Biomarker development must be prioritized in parallel with treatments

**Characteristics of Biomarkers**
- Associated with the illness of interest
- State-independent (present whether or not disease is active)
- Levels differ from those in the general population

**Categories of Biomarkers**
- Clinical
- Neuroimaging
- Genetic
- Biochemical

NIH Biomarkers Definitions Working Group
*Clin Pharm Ther* 69:89-95 2001
Biomarkers: General

- **Diagnostic Biomarkers**
  - Identification of individuals with disease
  - Early detection in pre-clinical or subclinical states
  - Staging/classifying extent of disease
    - Reduction of heterogeneity in clinical trials
  - Monitor therapeutic efficacy
    - Comparative effectiveness research
    - Assess differential efficacy

- **Predictive Biomarkers**
  - Indicator of disease prognosis
  - Prediction of clinical course

NIH Biomarkers Definitions Working Group
*Clin Pharm Ther* 69:89-95 2001
Biomarkers: Complementary Markers

- Clinical outcomes are complex—not all treatment effects can be fully captured by any single biomarker.
- Interventions may have adverse effects not detected by a single biomarker.

- Using multiple biomarkers to assess various components of a complex process may provide a more comprehensive assessment.

NIH Biomarkers Definitions Working Group

Clin Pharm Ther 69:89-95 2001
Biomarkers: Ideal Performance Evaluation

- **Analytical validation**
  - Test assay vs laboratory standards
  - Accuracy (agreement with reference)
  - Precision (reproducibility)
  - Sensitivity/specificity

- **Clinical validation**
  - Retrospective/prospective studies
  - Accuracy (agreement with clinical endpoint)
  - Precision (reproducibility)
  - Sensitivity/specificity
  - PPV/NPV for predictive biomarkers

- **Clinical performance**
Biomarkers:
Examples by Medium

- **Biological fluids or tissue**
  - Blood (basic chemistries, CRP, PSA, etc.)
  - Urine (β-hCG)
  - CSF
  - Nerve, muscle, skin, etc.

- **Physiological parameters**
  - EKG
  - PFTs

- **Imaging**
  - MRI, PET, bone scans, etc.

- **Clinical**
  - Pain scales
  - Psychometric testing
  - Apgar scores
Biomarkers of Hydrocephalus: An Impossible Dream?

Jack Ladenson, Ph.D.
Professor of Pathology and Immunology
and Laboratory Medicine
Washington University School of Medicine

- Developed the quantitative assays for CK-MB and Troponin C used universally for detection of myocardial infarction
- These biomarkers remain sensitive & specific in the setting of systemic diseases, neurological injuries, and even other known cardiac conditions
- Probably the best example of serum biomarkers accurately identifying a serious major medical condition

Considerations for a blood marker of cell death:

I. Sensitivity
- Abundance in cell
- Location in cell

II. Sample timing
- Mode of entry into blood
- Half-life of elimination

III. Specificity
- Distribution in different cells or organs

Ladenson JH  *Clin Chim Acta* 381:3-8, 2007
Biomarkers:
Applications in Hydrocephalus

- Facilitate diagnosis
  - Objective data for diagnosis confirmation
    - Reduce bias or subjectivity
    - Increase the probability of correct diagnosis
  - Early diagnosis/early intervention

- Monitor disease course, and

- Assess therapeutic response

- Differential efficacy/clinical trials
  - Reduce heterogeneity in clinical trials
  - Role in comparative effectiveness research (e.g. shunt vs ETV)

- Prognosis/anticipate long-term outcome
Biomarkers in Hydrocephalus: Accelerating Biomarker Development

**Biobanking**
- Standardized protocols and specimen handling
- Applicability across institutions
- HCRN Neonatal CSF Repository at Wash U

**Imaging**
- Conventional, advanced

**“omics” technologies** (genomics, proteomics, etc.)
- Bioinformatics
- Validate with conventional laboratory techniques

**Clinical/experimental record-keeping**
- Monitor clinical endpoints (e.g. need for shunt/ETV, shunt revision)
- Psychometrics / Neurodevelopmental outcomes
Biomarkers

Priority 1: Facilitate Diagnosis of Hydrocephalus

Two school-age boys, neurologically normal, present with >1 year of HA.

Subject 1

Is it hydrocephalus???

No

Subject 2

Is it hydrocephalus???

Yes!
Biomarkers

Priority 1: Facilitate Diagnosis of Hydrocephalus

**Subject 1:** 3 yo female with h/o Grade III IVH

- Diagnosed with cerebral palsy, speech delay
- 8 surgeries/3 years: VP shunt, valve change, shunt removal, ETV, shunt replacement, shunt ligation, reversal of ligation, 2 valves in series
- Outcome: motor and speech delays remain

Hydrocephalus?
Not Hydrocephalus?
Arrested/Compensated Hydrocephalus?
## Candidate Biomarkers: Hydrocephalus of Various Etiologies

**TNF-α Jimenez**

<table>
<thead>
<tr>
<th>Marker(s)</th>
<th>Authors</th>
<th>Year</th>
<th>Org</th>
<th>Medium Site</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tau, Aβ</td>
<td>Talab et al.</td>
<td>2009</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>15</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>TGF-β1/2</td>
<td>Douglas et al.</td>
<td>2009</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>27</td>
<td>Predict shunt req. in SAH</td>
</tr>
<tr>
<td>Cleaved tau</td>
<td>Cengiz et al.</td>
<td>2008</td>
<td>Human</td>
<td>CSF lum, vent</td>
<td>12</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Tenascin-C</td>
<td>Suzuki et al.</td>
<td>2008</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>36</td>
<td>Predict shunt req. in SAH</td>
</tr>
<tr>
<td>Tau, NFL, VIP, NPY, alb, others</td>
<td>Tisell et al.</td>
<td>2004</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>37</td>
<td>Diagnosis, Clinical</td>
</tr>
<tr>
<td>S-100b, GFAP Not MBP or NSE</td>
<td>Beems et al.</td>
<td>2003</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>41</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>MBP</td>
<td>Longatti et al.</td>
<td>1993</td>
<td>Human</td>
<td>CSF lum, vent</td>
<td>17</td>
<td>Diagnosis</td>
</tr>
</tbody>
</table>
## Candidate Biomarkers: NPH

<table>
<thead>
<tr>
<th>Marker(s)</th>
<th>Authors</th>
<th>Year</th>
<th>Org</th>
<th>Medium Site</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>sAPP, tau, Aβ, APPs</td>
<td>Miyajima et al.</td>
<td>2012</td>
<td>Human</td>
<td>CSF, lumbar</td>
<td>uk</td>
<td>Diagnosis, Cognition</td>
</tr>
<tr>
<td>Tf-2/Tf-1 ratio Transferrin glycan</td>
<td>Futakawa et al.</td>
<td>2012</td>
<td>Human</td>
<td>CSF, lumbar</td>
<td>29</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Combined tau &amp; Aβ</td>
<td>Tarnaris et al.</td>
<td>2011</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>22</td>
<td>Diagnosis, Clinical</td>
</tr>
<tr>
<td>α2HSGP, others (Proteomics)</td>
<td>Scollato et al.</td>
<td>2010</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>17</td>
<td>Therapeutic Response</td>
</tr>
<tr>
<td>TGF-β1, LRG TGF-βR-II</td>
<td>Li et al.</td>
<td>2007</td>
<td>Human</td>
<td>CSF lumbar</td>
<td>35</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>NFL, tau, Aβ42 Not sulfatide</td>
<td>Agren-Wilsson et al.</td>
<td>2007</td>
<td>Human</td>
<td>CSF lumbar</td>
<td>111</td>
<td>Diagnosis</td>
</tr>
</tbody>
</table>
## Candidate Biomarkers: NPH

<table>
<thead>
<tr>
<th>Marker(s)</th>
<th>Authors</th>
<th>Year</th>
<th>Org</th>
<th>Medium Site</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFL</td>
<td>Tullberg et al.</td>
<td>2007</td>
<td>Human</td>
<td>CSF lum and vent</td>
<td>35</td>
<td>Predict PVH, clinical outcome</td>
</tr>
<tr>
<td>LRG, others (Proteomics)</td>
<td>Li et al.</td>
<td>2006</td>
<td>Human</td>
<td>CSF lumbar</td>
<td>27</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>TBAR free-rad perox</td>
<td>Fersten et al.</td>
<td>2004</td>
<td>Human</td>
<td>CSF lumbar</td>
<td>24</td>
<td>Diagnosis Cognition</td>
</tr>
<tr>
<td>beta-trace</td>
<td>Mase et al.</td>
<td>2003</td>
<td>Human</td>
<td>CSF lumbar</td>
<td>28</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>tau</td>
<td>Kudo et al.</td>
<td>2000</td>
<td>Human</td>
<td>CSF lumbar</td>
<td>20</td>
<td>Diagnosis, Clinical</td>
</tr>
</tbody>
</table>
Biomarkers

Priority 1: Facilitate Diagnosis of Hydrocephalus

No Known Neurological Disease

Grade III IVH Reservoir, no shunt

Grade IV IVH No surgery

Grade IV IVH Reservoir, VP shunt
### Candidate Biomarkers: PHH

<table>
<thead>
<tr>
<th>Marker(s)</th>
<th>Authors</th>
<th>Year</th>
<th>Org</th>
<th>Medium Site</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP, brevican, NCAM, L1CAM</td>
<td>Morales et al.</td>
<td>2012</td>
<td>Human</td>
<td>CSF lum, vent</td>
<td>24</td>
<td>Diagnosis, Ther. response</td>
</tr>
<tr>
<td>sFAS sfas lig, aCasp 3</td>
<td>Schmitz et al. Felderhoff-Mueser et al.</td>
<td>2011, 2003, 2001</td>
<td>Human</td>
<td>CSF lum, vent</td>
<td>29, 22, 31</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Lipina et al.</td>
<td>2010</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>29</td>
<td>Predict ETV success</td>
</tr>
<tr>
<td>IL-1β, IL-18, Inf-γ</td>
<td>Schmitz et al.</td>
<td>2007</td>
<td>Human</td>
<td>CSF ventricle</td>
<td>47</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Nitrated CSPG</td>
<td>Krueger RC</td>
<td>2004</td>
<td>Human</td>
<td>CSF lum, vent</td>
<td>29</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>VEGF Not TGF-β1</td>
<td>Heep et al.</td>
<td>2004</td>
<td>Human</td>
<td>CSF lum, vent</td>
<td>38</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Whitelaw et al.</td>
<td>1999</td>
<td>Human</td>
<td>CSF lum, vent</td>
<td>31</td>
<td>Diagnosis, Ther. response</td>
</tr>
</tbody>
</table>
Biomarkers of Hydrocephalus

Priority 2: Accurately Identify Shunt Malfunction

Subject 1: 18 yo male with PHH presents with HA

Subject 2: 19 yo male with PHH presents with HA

Functional Shunt

Shunt Malfunction

Is it the shunt???

Yes!
Biomarkers of Hydrocephalus
Priority 3: Early Detection

25 wk EGA male

27 wk EGA male

8 weeks

10 days
Early versus late treatment of posthaemorrhagic ventricular dilatation:
results of a retrospective study from five neonatal intensive care units
in The Netherlands

LS de Vries¹, KD Liem², K van Dijk², BJ Smit³, L Sie⁴, KJ Rademaker¹ and AWD Gavilanes⁵; on behalf of
the Dutch Working Group of Neonatal Neurology

- 95 preterm infants ≤ 34 weeks EGA with PHH
- Early intervention: ventricular index ≥ 97%
  - 31 infants
  - 5/31 (16.1%) required VP shunts
- Late intervention: ventricular index ≥ 97% + 4mm
  - 42 infants

Table 1. Neurodevelopmental outcome at 24 mo of the 95 infants with posthaemorrhagic ventricular dilatation (PHVD).

<table>
<thead>
<tr>
<th></th>
<th>No intervention (n = 22)</th>
<th>Early intervention (n = 31)</th>
<th>Late intervention (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>14</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Mild disability</td>
<td>5</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
Randomized Trial of Drainage, Irrigation and Fibrinolytic Therapy for Premature Infants with Posthemorrhagic Ventricular Dilatation: Developmental Outcome at 2 years

- **DRIFT Trial**: 77 preterm infants
- **Neurodevelopmental disability 2 years**
  - **Severe disability**
    - DRIFT: 21/39 (54%)
    - Standard: 27/38 (71%)

### TABLE 2 Effect of DRIFT on the Distribution of Bayley Developmental Indices

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Severe Disability (&lt;55)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DRIFT</td>
</tr>
<tr>
<td>MDI</td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td>8 (23)</td>
</tr>
<tr>
<td>70–84</td>
<td>9 (26)</td>
</tr>
<tr>
<td>55–69</td>
<td>7 (20)</td>
</tr>
<tr>
<td>&lt;55</td>
<td>11 (31)</td>
</tr>
<tr>
<td>PDI</td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td>4 (12)</td>
</tr>
<tr>
<td>70–84</td>
<td>5 (15)</td>
</tr>
<tr>
<td>55–69</td>
<td>11 (32)</td>
</tr>
<tr>
<td>&lt;55</td>
<td>14 (41)</td>
</tr>
</tbody>
</table>
Post-hemorrhagic Hydrocephalus: Does Early Intervention Improve Outcome?

Biomarkers of Hydrocephalus

**Priority 4: Monitoring Therapeutic Response**

- Physiology/functional
  - aEEG
  - AFP

- Blood flow:
  - TCDs, NIRS, optical tomography

- MRI
  - MRA, ASL
  - rs fc MRI

- CSF/serum biomarkers

- Other
# Candidate Biomarkers: Functional Parameters

<table>
<thead>
<tr>
<th>Marker(s)</th>
<th>Authors</th>
<th>Year</th>
<th>Etiol</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>aEEG</td>
<td>Olischar et al.</td>
<td>2009</td>
<td>PHH</td>
<td>12</td>
<td>Ventr. Size Clinical signs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2004</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PI, RI, CBFV TCDs</td>
<td>Rainov et al.</td>
<td>2000</td>
<td>Adult</td>
<td>49</td>
<td>ICP, therapeutic response</td>
</tr>
<tr>
<td>PI, RI TCDs</td>
<td>Hanlo et al. Goh &amp; Minns</td>
<td>1995</td>
<td>Infantile</td>
<td>---</td>
<td>ICP, shunt requirement</td>
</tr>
<tr>
<td></td>
<td>Hanlo et al.</td>
<td>1995</td>
<td>Infantile</td>
<td>37</td>
<td>Correl. with clinical signs</td>
</tr>
<tr>
<td>Anterior fontanel pressure</td>
<td>Hanlo et al.</td>
<td>1996</td>
<td>Infantile</td>
<td>37</td>
<td>Correl. with clinical signs</td>
</tr>
</tbody>
</table>
## Candidate Biomarkers: MRI

<table>
<thead>
<tr>
<th>Technique</th>
<th>Authors</th>
<th>Year</th>
<th>Etiol</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTI</td>
<td>Air et al.</td>
<td>2010</td>
<td>Varied</td>
<td>10</td>
<td>Therapeutic response</td>
</tr>
<tr>
<td>DTI MRA/CBF</td>
<td>Leliefeld et al.</td>
<td>2010</td>
<td>Comp. HC</td>
<td>18</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>DTI</td>
<td>Leliefeld et al.</td>
<td>2009</td>
<td>Varied</td>
<td>24</td>
<td>Therapeutic response</td>
</tr>
<tr>
<td>DTI</td>
<td>Leliefeld et al.</td>
<td>2009</td>
<td>Varied</td>
<td>24</td>
<td>Therapeutic response</td>
</tr>
<tr>
<td>DTI</td>
<td>Ng et al.</td>
<td>2009</td>
<td>NPH</td>
<td>9</td>
<td>Diagnosis, Therapeutic response</td>
</tr>
<tr>
<td>trueFISP</td>
<td>Hodel et al.</td>
<td>2009</td>
<td>Obstr. HC</td>
<td>26</td>
<td>Therapeutic response</td>
</tr>
<tr>
<td>MRA/CBF</td>
<td>Leliefeld et al.</td>
<td>2008</td>
<td>Varied</td>
<td>15</td>
<td>ICP, Therapeutic response</td>
</tr>
<tr>
<td>PC CSF flow</td>
<td>Stvaros et al.</td>
<td>2009</td>
<td>Obstr. HC</td>
<td>26</td>
<td>Therapeutic response</td>
</tr>
<tr>
<td>MRS: lact:Cr</td>
<td>Del Mar Matarin et al.</td>
<td>2007</td>
<td>NPH</td>
<td>12</td>
<td>Clinical, psychometrics</td>
</tr>
</tbody>
</table>
Post-hemorrhagic Hydrocephalus: CSF APP vs Ventricular Size

Subject 1

Subject 2
Biomarkers of Hydrocephalus

Priority 5: Anticipating Outcome

- Psychometrics
- Serum/CSF Biomarkers
- MRI
  - Volumetric analysis
  - Surface morphometry/gyrification index
  - MR spectroscopy
  - rs fc MRI?
  - DTI
Advanced MRI: Diffusion Tensor Imaging

- Non-invasive measure of white matter integrity
  - Detects WM injury in the absence of structural damage, e.g. damage to axonal membrane, myelin

- DTI measures the magnitude and directionality of water displacement
  - Provides a tensor & eigenvector of white matter tracts

- Fractional anisotropy (FA) and mean diffusivity (MD) are quantifiable parameters
  - FA and MD correlate with cognitive function
Longitudinal comparison of pre- and postoperative diffusion tensor imaging parameters in young children with hydrocephalus


ELLEN L. AIR, M.D., PH.D.,1,5 WENHONG YUAN, PH.D.,5 SCOTT K. HOLLAND, PH.D.,5
BLAISE V. JONES, M.D.,3 KARIN BIERBRAUER, M.D.,1,5 MEKIBIB ALTAYE, PH.D.,4
AND FRANCESCO T. MANGANO, D.O.1,5
Diffusion Tensor Imaging

Pre-ETV FOR = 0.59
Post-ETV FOR = 0.59

# Neuropsychological Metrics

<table>
<thead>
<tr>
<th></th>
<th>Pre-op</th>
<th>3 months post-op</th>
<th>14 months post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABAS-II (SS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Conceptual Ability (GCA)</td>
<td>89</td>
<td>101</td>
<td>99</td>
</tr>
<tr>
<td>Conceptual</td>
<td>109</td>
<td>113</td>
<td>115</td>
</tr>
<tr>
<td>Social</td>
<td>90</td>
<td>108</td>
<td>99</td>
</tr>
<tr>
<td>Practical</td>
<td>86</td>
<td>96</td>
<td>84</td>
</tr>
<tr>
<td>Motor</td>
<td>95</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td><strong>CBCL (T)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td>52</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>Externalizing</td>
<td>52</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>Total problems</td>
<td>57</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td><strong>Bayley-3 (SS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td></td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td>97</td>
<td></td>
</tr>
<tr>
<td><strong>WPPSI-III (SS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full IQ</td>
<td></td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td></td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Performance</td>
<td></td>
<td>97</td>
<td></td>
</tr>
<tr>
<td><strong>VMI (SS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMI</td>
<td></td>
<td>88</td>
<td>78</td>
</tr>
</tbody>
</table>

Genu CC

Longitudinal DTI in Pediatric HC

PLIC

Neuropsych

Yaun et al. *AJNR* in press
Biomarkers of Hydrocephalus: A Clear Pathway to Better Outcomes

- Identify consensus priorities for coordinated, focused biomarker development
- Validate promising biomarkers through multi-institutional networks to accelerate clinical implementation
- Advocate for funding to support technology and provide resources for biomarker discovery (e.g. proteomics)
- Establish repositories for clinical parameters, imaging, and biological tissues/fluids for patients in whom hydrocephalus is considered
- Consider each clinical trial an opportunity for biomarker development!
Richard Morrison, Ph.D.

Education
- B.S. USC
- Ph.D. UCLA
- Post-doc UC-Irvine

Current Position
- Staatz Professor
- Director, Center for Neuroproteomics
- University of Washington

“Proteomic characterization of human ventricular cerebrospinal fluid from patients with hydrocephalus.”
Laurence Watkins, M.D.

Education
Cambridge University
Atkinson Morley’s/Queen Square/Great Ormand Street

Current Position
Consultant Neurosurgeon
Program Director, Neurosurgical Training
National Hospital for Neurology and Neurosurgery

“Biomarkers of NPH – molecules and other predictors of outcome.”
Acknowledgments

- NIH/NINDS 1 K23 NS075151-01A1
- NINDS 1R01NS066932-01 (PIs Mangano, Yuan)
- Hydrocephalus Clinical Research Network / PHH CSF Repository
- CTSA Grant UL1 RR024992
- CTSA/ICTS JIT Award
- Children’s Surgical Sciences Institute Faculty Development Award
- Mentors: Dave Holtzman, Terrie Inder, Ralph Dacey, TS Park
- Laboratory research: Diego Morales, Haejun Ahn, Shawgi Silver
- Clinical research assistant: Deanna Mercer
Additional Slides
Purification of Low-Abundance CSF Proteins

- IgY-14 Immunoaffinity Column
  - Extraction of HAPs
    - HSA
    - IgG
    - Fibrinogen
    - Transferrin
    - Others

- Supermix Immunoaffinity Column
  - Extraction of MAPs
    - Transthyretin
    - Complement factors
    - Ceruplasmin
    - Others

Flow-through fraction
  - Contains LAPs

Eluted fraction
  - Contains MAPs

Biomarkers
Quantitative Proteomics

Immunodepleted CSF samples

In-solution protease digestion of proteins (trypsin, LysC)

LTQ Orbitrap
  • HPLC
  • Mass spectrometer

Protein Quantification & Analysis

Peptide Identification

Peak alignment of mass chromatograms

Protein Mediators of Neurodevelopment
CSF Protein Elevations are Specific for PHH

n = 4 for each group
Correlation of APP and FOR:
\[ R = 0.87 \]
\[ p = 0.003 \]

Correlation of NCAM1 and FOR:
\[ R = 0.86 \]
\[ p = 0.003 \]
Protein Mediators of Neurodevelopment: Dose-dependent Paradoxical Effects

- **APP**
  - Marker of axonal injury
  - Precursor to amyloid-β (senile plaques in AD)

- **Brevican**
  - Deposition in HIE
  - Inhibits synaptogenesis, plasticity
  - Glial scar formation/PVL

- **NCAM1**
  - Involved in inflammatory mechanisms implicated in neurodegeneration

- **L1CAM**
  - Mutations cause hydrocephalus, cerebral anomalies, MR, LE spasticity

Are PHH-related increases in these proteins contributing to neurodevelopmental impairments?
Periventricular L1CAM: Hypothesis: Transudative Deposition

- Impairment of neurite outgrowth?
- Impairment of neural precursor cell proliferation/differentiation/migration?
Periventricular L1CAM:
Hypothesis: Transudative Deposition