Biomarkers of NPH – molecules and other predictors of outcome

Laurence Watkins
Victor Horsley Department of Neurosurgery
National Hospital for Neurology & Neurosurgery
Queen Square, London
U.K.
Normal pressure hydrocephalus

- Classical triad
  - Gait disturbance
  - Urinary incontinence
  - Cognitive decline
Other features

- Impaired wakefulness is associated with reduced anterior cingulate CBF in patients with normal pressure hydrocephalus.

Normal pressure hydrocephalus

- First named 48 years ago by Salomon Hakim

Some Observations on C.S.F. Pressure. Hydrocephalic Syndrome in Adults with "Normal" C.S.F. Pressure. (Recognition of a new syndrome.)

Salomon Hakim, M.D.
Thesis No. 957,
Javeriana University School of Medicine,
Bogotá, Colombia, S.A., March 10, 1964

Translated from Spanish:
Algunas Observaciones Sobre la Pression del L.C. R. Sindrome Hydrocepstico en el Adulto con "Presion Normal" del L.C.R.
(Presentacion de un Nuevo Sindrome)
NPH – history

“an occasional exceptional case is encountered in which the CSF spaces are closed and the ventricles progressively enlarge without the measured intraventricular pressure rising above 150-200 mm of water” (Penfield 1935)
NPH – the potential

- Common disease
- Treatable – CSF shunt
- Currently under-recognized & under-treated
How common is NPH?

- 1-10% of patients with dementia
How common is NPH?

- 0.4% of population over 65 years-old
  - Prevalence of Parkinson's disease and related disorders assessed by a *door-to-door survey* of inhabitants older than 65 years.
International consensus guidelines on diagnosis & management

Management of Normal Pressure Hydrocephalus: Diagnosis

Degree of Certainty for Improvement Sensitivity

Clinical exam → Triad element present
- NO: Follow
- YES: Evaluate surgical candidacy

Evaluate surgical candidacy → LP CSF bolus withdrawal
- Improved
  - ICP > 18: Probable secondary hydrocephalus
  - ICP 5 - 18: CSF dynamics test
    - Ro↑: Drainage protocol
      - +: Shunt
      - -: Follow
    - Ro↓: Follow
- NO: Follow
Extended lumbar drainage protocol

- “Gold standard” diagnostic and predictive test
- Invasive
- Resource use – inpatient days
- Difficult to repeat to track progress
- Difficult to perform on controls
Biomarkers of disease & injury

- measurable characteristics
- used to track biological processes
  - Diagnosis
    - Risk
    - Clinical decisions
  - Progression
  - Response to treatment
Biomarkers

- Measurable characteristics
- Imaging – quantitative
  - Volumetric
  - Spectroscopy
- Chemical
  - In vivo factors
  - Tissue
  - Biofluids – CSF (blood, urine)
Biomarker technology

- ELISA kits – in house or commercial
- Protein microarrays
- Mass spectroscopy proteomics
- Microfluidics – “lab on a chip”
- Example - PSA
Translational research strategies

- Cohorts
- Stratification
- Biobanks
- Personalized medicine
- Biomarkers can help
CSF biomarkers

- Peptides
- Neurotransmitters
- Metabolites
- Proteins especially enzymes
Most promising

- Tau protein
- Amyloid beta
- Tumor necrosis factor
- Lactate
- Sulfatide
- Neurofilament triple protein
Review of literature

CSF biomarkers in NPH vs Alzheimer’s

- Neuropeptides
  - Somatostatin
  - Vasoactive intestinal peptide
  - δ-sleep-inducing peptide
  - Neuropeptide Y
  - Vasopressin
  - Diazepam-binding inhibitor receptor
  - Peptide YY
  - Cystatin C
CSF biomarkers in NPH vs Alzheimer’s

- **Neurotransmitters**
  - 3-methoxy-4-hydroxyphenylglycol
  - Homovanillic acid

- **Cerebral metabolites**
  - Lactate
  - 3-methoxy-4-hydroxyphenylglycol
  - 5-hydroxyindoleacetic acid
CSF biomarkers in NPH vs Alzheimer’s

- **Enzymes**
  - Neuron-specific enolase
  - Acetylcholinesterase
  - Butyrylcholinesterase
  - Lipocalin-type prostaglandin D synthase (β-trace)
CSF biomarkers in NPH vs Alzheimer’s

- Neural cell-derived proteins
  - S100
  - Phosphorylated and total tau
  - β-amyloid 1-40 and 1-42
  - Glial fibrillary acidic protein
  - Gp D2
  - Myelin basic protein
  - Brain-derived neurotrophic factor
CSF biomarkers in NPH vs Alzheimer’s

- **Cytokines**
  - IL-1
  - IL-10
  - IL-12
  - IFN-γ
  - TGF-1

- **Others**
  - β₂-microglobulin
  - Transthyretin
  - Adenyl cyclase
Difficulties

- Cerebral to lumbar gradient
Difficulties

- Variation with collection technique and individual CSF production rate
- Trend towards ratios and panels of biomarkers
- For research protocols should we measure CSF production rate?
Difficulties

- Some peptides adhere to silicone and other plastics
- Rapidly degrade
- **Protocol**: polypropylene tubes and transferred to laboratory for -80C freezing within 2 hours of collection
Most promising

- Tau protein
- Amyloid beta
- Tumor necrosis factor
- Lactate
- Sulfatide
- Neurofilament triple protein
Success story – Tau and Abeta

- local ranges derived from:
- 100 (non-neurodegenerative) controls
- 100 Alzheimer's disease subjects
- 100 with non-Alzheimer's neurodegenerative clinical diagnoses (mainly FTD, PSP and CBD)
Success story – Tau and Abeta

- CSF Abeta 1-42 is reduced in Alzheimer's disease and in other causes of cerebral Abeta deposition (e.g. some patients with Dementia and Lewy Bodies (DLB)). CSF total Tau may also be increased in Alzheimer's but can also be raised in other causes of neuronal damage.
Success story – Tau and Abeta

- A high Tau/ABeta ratio is significantly associated with Alzheimer's, and (less strongly) with other neurodegenerative illnesses.
- Less potential for benefit from shunt insertion in NPH.
- Now routine in NPH assessment.
Promising candidate

- Tumor necrosis factor
- Inflammatory mediator
- Tarkowski, Tullberg et al. 2003
- TNF-α in NPH patients (n= 35)
- Compared them with controls
- NPH group levels were 45-fold higher
- TNF-α returned to control levels
- Following shunting in the group that improved following surgery
Promising candidate

- Neurofilament protein
- Large unmyelinated axons
- ? Marker of white matter damage
- Raised in NPH and vascular dementia
- Does not differentiate between those diagnoses
Promising candidate

- Lactate
- Lactate levels lower in NPH and AD
- Does not differentiate between those diagnoses
Promising candidate

- Sulfatide
- glycosphingolipid component of myelin
- cutoff level 400 nmol/L can distinguish NPH (lower) and SIVD (higher) with a sensitivity of 74% and specificity of 94%
- Agren-Wilsson (2007)
- No difference (cohort homogeneity?)
Abnormal cilia?
Huntington disease (HD)

- Htt regulates ciliogenesis
- Loss of Htt in mouse cells reduced primary cilia formation
- In mice, deletion of Htt in ependymal cells led to alteration of the cilia layer, and hydrocephalus
Huntington disease (HD)

- PCM1 accumulation in ependymal cells was associated with longer cilia and disorganized cilia layers in a mouse model of HD and in HD patients.
- Longer cilia resulted in alteration of the cerebrospinal fluid flow.
Fluid dynamics

Laminar

Free Stream

Turbulent

Velocity

Boundary Layer

Surface of Object

Velocity is zero at the surface (no-slip)
Hydrocephalus paradigms

- Mass flow
- Pulsatility
- Boundary layer/cilia?
- Biomarkers of the huntingtin-
  HAP1-PCM1 pathway?
Translational research strategies

- Cohorts
- Stratification
- Biobanks
- Personalized medicine
- Biomarkers can help
Thank you

laurence.watkins@uclh.nhs.uk