

# Biomarkers of NPH – molecules and other predictors of outcome

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# 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.
- *Tullberg, M.; Hellstrom, P.; Piechnik, S. K.; Starmark, J.-E.; Wikkelso, C. Acta Neurologica Scandinavica. 110(5):322-330, 2004.*

# 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 Presión del L.C. R. Síndrome Hidrocefálico en el Adulto con "Presión Normal" del L.C.R. (Presentación de un Nuevo Síndrome)**

## 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

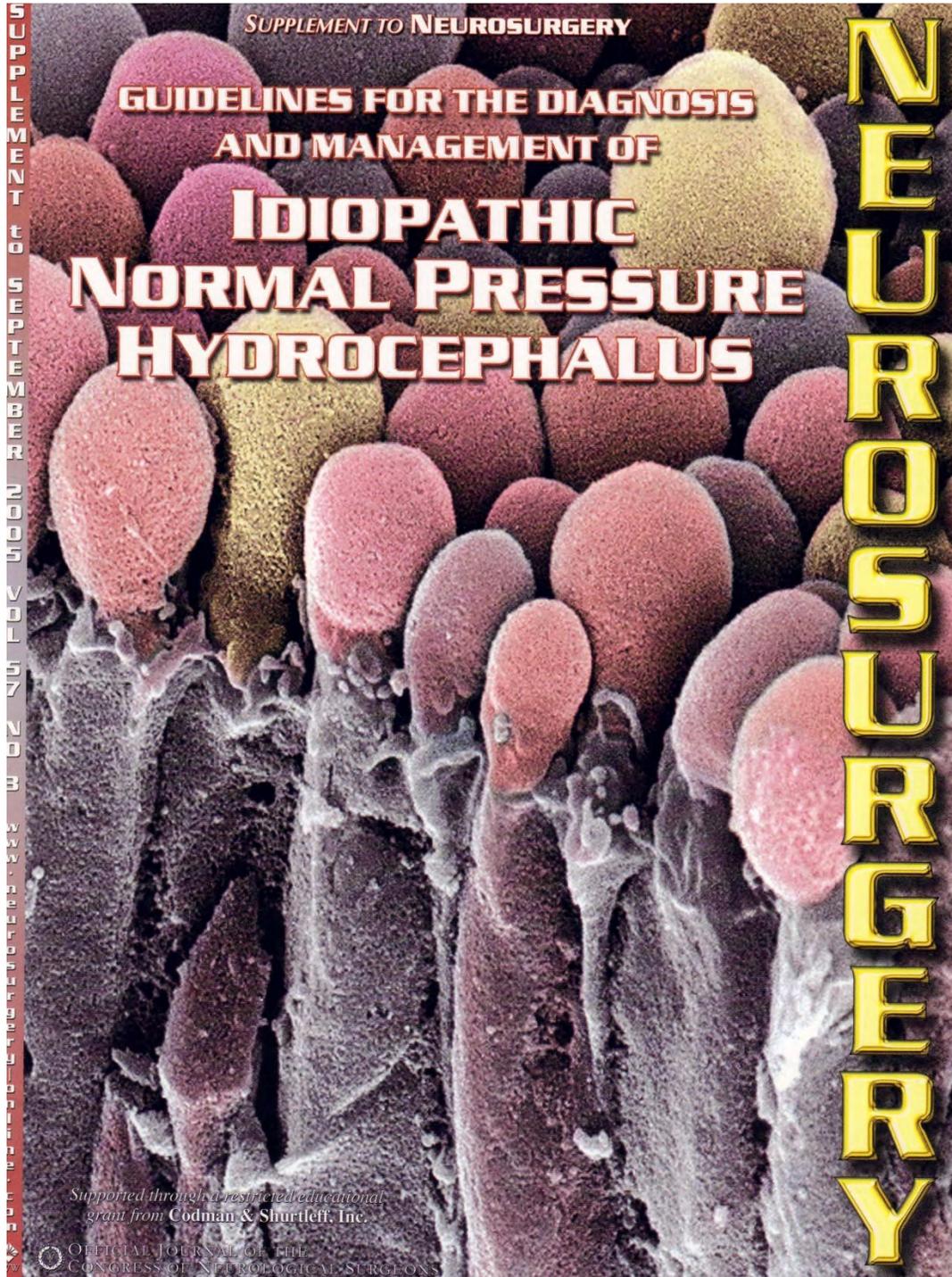
- Common disease
- Treatable – CSF shunt
- Currently under-recognized & under-treated

# How common is NPH?

- 1-10% of patients with dementia
- Larson EB, Reifler BV, Featherstone HJ, English DR: Dementia in elderly outpatients: a prospective study. *Ann Intern Med* 1984; **100(3)**:417-423.

# How common is NPH?

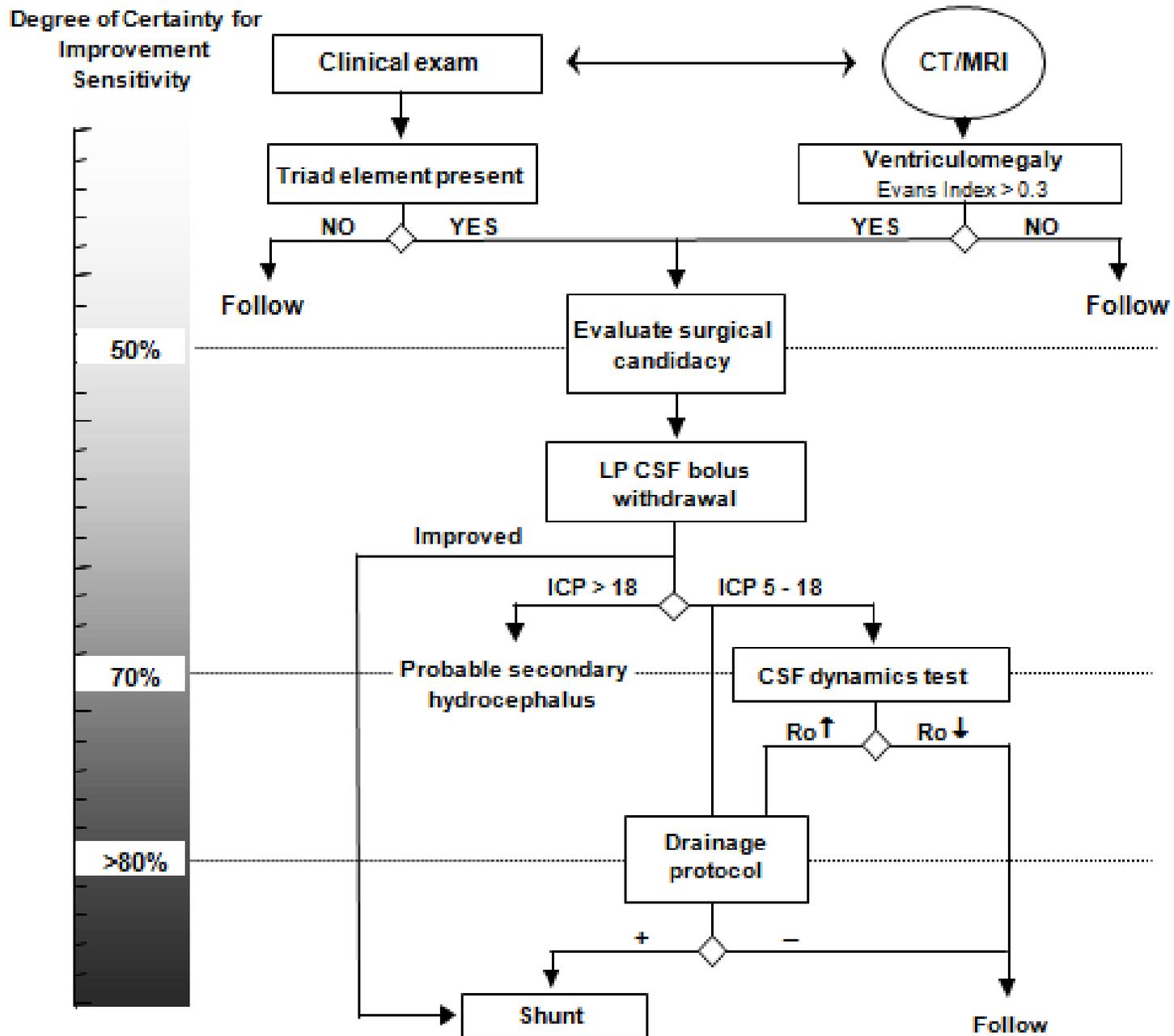
- **0.4% of population over 65 years-old**
  - ◆ Trenkwalder C, Schwarz J, Gebhard J, Ruland D, Trenkwalder P, Hense HW, et al.
  - ◆ Prevalence of Parkinson's disease and related disorders assessed by a **door-to-door survey** of inhabitants older than 65 years.
  - ◆ Arch Neurol. 1995;52(10):1017-22



International consensus  
guidelines on diagnosis &  
management

*57(3) Supplement:S2-40-S2-52,  
September 2005.*

# Management of Normal Pressure Hydrocephalus: Diagnosis



# 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

- Tarnaris A, Toma AK, Kitchen ND, Watkins LD. Ongoing search for diagnostic biomarkers in idiopathic normal pressure hydrocephalus. *Biomarkers in Medicine* 2009 Dec; 3 (6):787-805

# CSF biomarkers in NPH vs Alzheimer's

- **Neuropeptides**
  - ◆ Somatostatin
  - ◆ Vasoactive intestinal peptide
  - ◆  $\delta$ -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 ( $\beta$ -trace)

# CSF biomarkers in NPH vs Alzheimer's

## ■ **Neural cell-derived proteins**

- ◆ S100
- ◆ Phosphorylated and total tau
- ◆  $\beta$ -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- $\gamma$
- ◆ TGF-1

## ■ Others

- ◆  $\beta_2$ -microglobulin
- ◆ Transthyretin
- ◆ Adenyl cyclase

# Difficulties

- Cerebral to lumbar **gradient**
- Tarnaris A, Toma AK, et al. (2009). "The longitudinal profile of CSF markers during external lumbar drainage." *Journal of Neurology, Neurosurgery & Psychiatry* **80(10): 1130-1133**

# 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- $\alpha$  in NPH patients (n= 35 )
- compared them with controls
- NPH group levels were 45-fold higher
- TNF-  $\alpha$  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

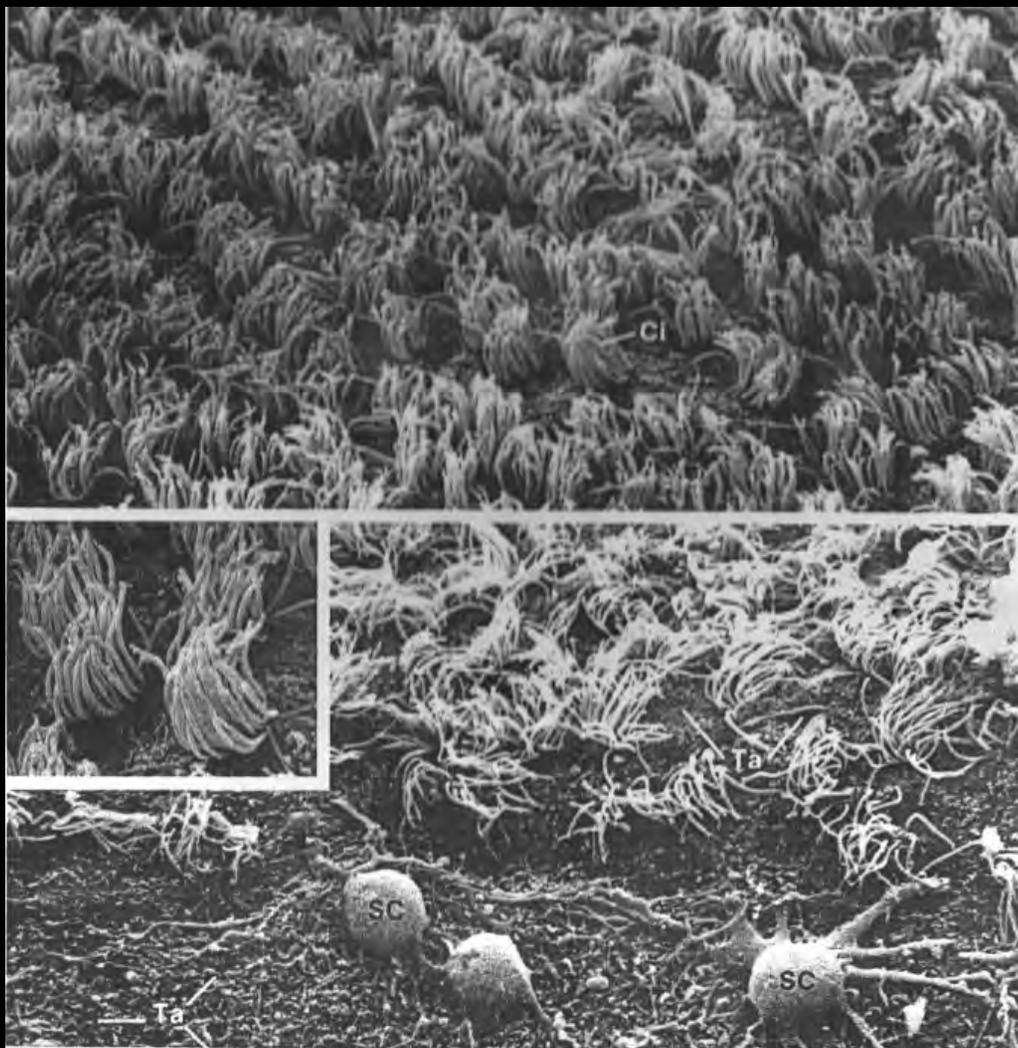
# Promising candidate

- **Lactate**
- Malm J, et al (1991)
- Lactate levels lower in NPH and AD
- Does not differentiate between those diagnoses

# Promising candidate

- **Sulfatide**
- glycosphingolipid component of myelin
- Tullberg et al (2000)
- 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?



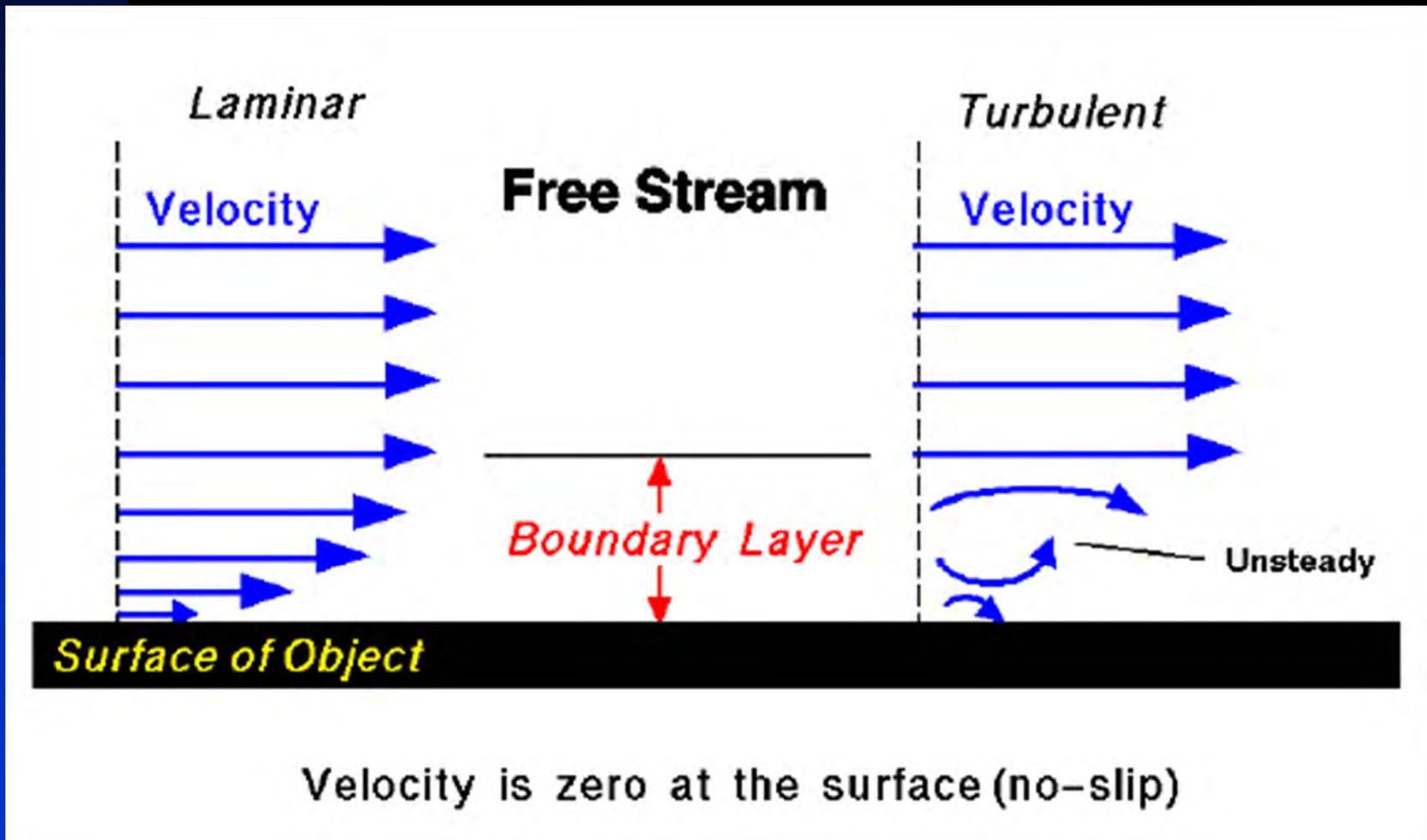
# Huntington disease (HD)

- **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

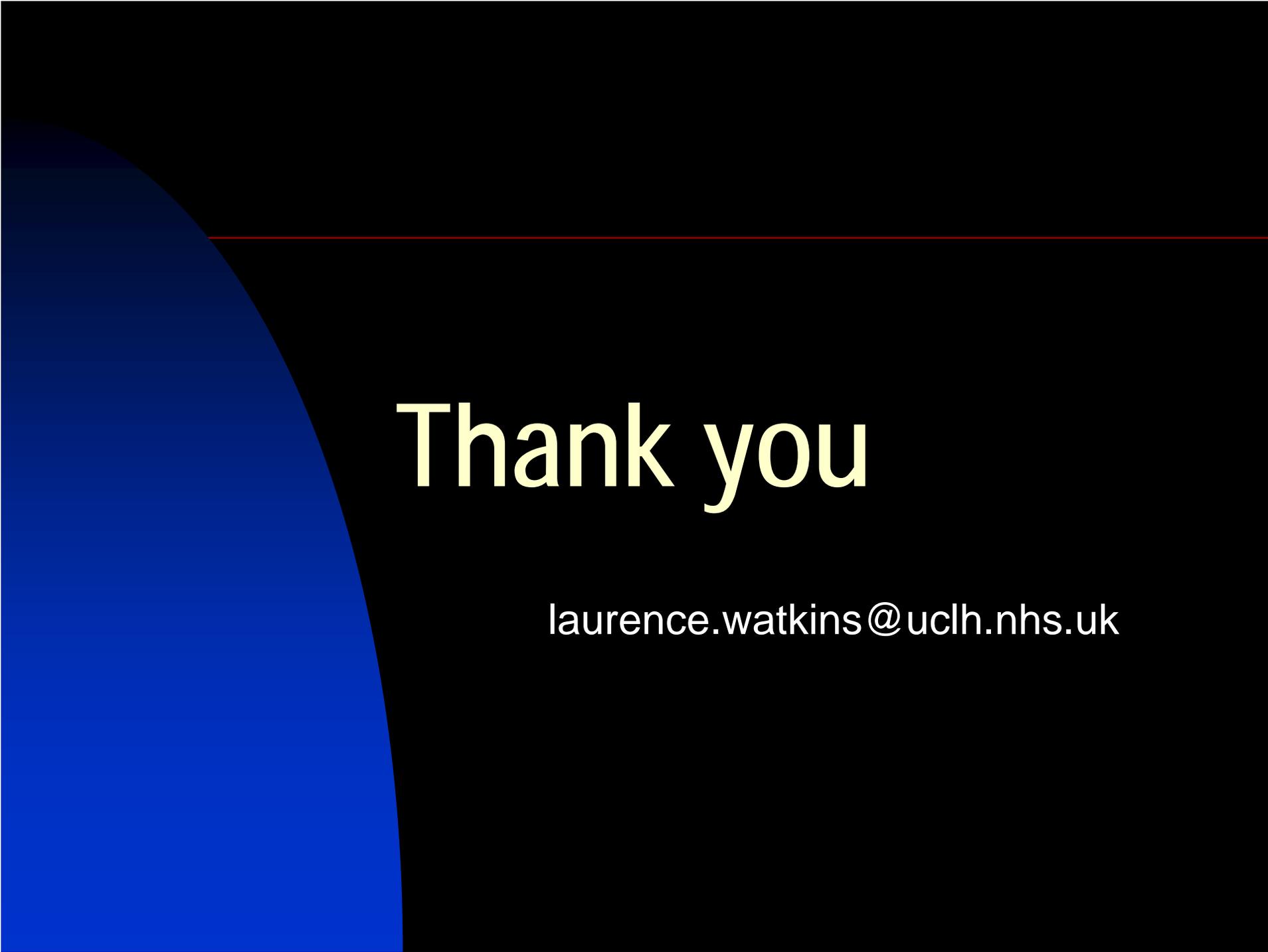


# Hydrocephalus paradigms

- 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

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