TIMESLIP in Normal Pressure Hydrocephalus, Dementia, CSF & Interstitial Glymphatic Flow

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Outline

- Hypothesis: BBB, Brain Perfusion, Glymphatics & Brain Compliance
  - Everything gets smaller and worse as you get older (Bill Bradley)
- Abnormal BBB DCE MRI in MCI and AD
  - Correlation with CSF markers and CSF flow (Zlokovic, Law, Chui et al)
- What is Normal flow of CSF and ISF?
  - Bulk flow?
  - Pulsatile flow? Diffusion Flow
  - Drainage of CSF – Relative contributions unknown from
    - Arachnoid granulations
    - Perineural nerve sheaths
    - Drainage into the dural lymphatics/glymphatics then neck
- Cine Phase Contrast & Time Slip Spin Imaging of CSF Flow

Vascular Contributions to AD @ USC

Consultant:
GE Healthcare, Fuji, Samsung Electronics

Speakers Bureau:
Siemens Medical Solutions

Toshiba Medical

Honorarium/Grants:
Bayer Healthcare
Bracco Diagnostics, iCAD Inc

Stockholder/Consultant:
Prism Clinical Imaging

Vascular – Alzheimer – NPH Spectrum

- Hypothesis: BBB, Brain Perfusion, Glymphatics & Brain Compliance
  - Everything decreases or gets worse as you get older
- Considerable overlap between 3 dementia phenotypes
- Aging and Vascular Risk Factors Contributions to Brain Aging
- Decreased Blood Flow, Glymphatic Drainage of Amyloid – Tau – AD
- Decreased Brain Compliance of BOTH ISF and CSF flow - NPH

THAT IS these ARE the same diseases along the dementia spectrum

Glymphatic dysfunction: Aging

- In aged mice, 80-90% reduction in glymphatic function
- Depolarization correlates with CSF-ISF exchange, suggesting glymphatic dysfunction partly due to dysregulation of astroglial water transport
- Additional contributing factors include:
  - 66% decline in CSF production
  - 27% decline in CSF pressure
  - Arterial wall stiffening → reduction in arterial pulsatility
CSF Flow – pulsatile/diffusion
Not bulk flow like blood vessels

Aging: Decreased Perfusion, Decreased Lymphatics, Decreased Compliance

Yamada S & Kelly E Seminars in US, CT and MRI 2016

Head Stationary (sleep)

CSF flow in 3rd and 4th but minimal flow into Lateral Ventrices
Shinya Yamada

Head move (awake)

Exercise increase CSF flow also arterial inflow, CSF-ISF gradient, venous/lymph outflow
Shinya Yamada

The two-hit vascular hypothesis for Alzheimer’s disease

Glymphatic flow decreased
With decreased brain flow
Impact on Brain Compliance
Note: NPH & AD

TESTING TW0 HIT VASCULAR HYPOTHESIS IN ANIMAL MODELS ON DIFFERENT APOE GENOTYPE

TRE knock-in mice
3 x Tg mice

14C-IAP autoradiography
2P imaging - perfused capillaries
STP analysis - 2D-lectin angiography
MRI analysis of perfused brain

Neuroimaging biomarkers
Pathways of BBB permeability in vivo
MRI analysis of BBB markers
High-resolution confocal analysis of brain tissue
Molecular analysis of CypA-MMP-9 pathway at the BBB
CSF analysis
Albumin (spatial; CypA, MMP9, POD, IA8)

Brain/CSF analysis
A42 (40), amyloid, tPtau
Plasma sLRP1

PDFGRb

Cognitive decline
Neural dysfunction and injury
Neurodegeneration

Functional connectivity
Labeling pathways
STP analysis of pathways
Voltage-sensitive dye
Electrophysiology
fMRI resting functional connectivity
Behavioral tests

Zilka Neurogenetic Institute

B Zlokovic Nature Neuroscience Dec 2011
**ApoE Aβ-independent functions**

**HUMAN DATA**
- APOE4 carriers: reductions in neurovascular functions (e.g., flow, glucose transport)
- AD - BBB breakdown more common in individuals with at least one APOE4 allele
- AD - collapsed vessels, reduced capillary density

**MOUSE DATA**
- Apoe-/-: BBB breakdown
- APOE4 - BBB susceptibility to injurious stimuli

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**BBB breakdown in the hippocampus in the living human brain during normal aging (Neuron 2015)**

BBB changes with age
- BBB changes with memory impairment
- BBB and APOE4
- BBB albumin and pericyte dysfunction

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**BBB breakdown in the hippocampus in the living human brain during normal aging (Neuron 2015)**

Age-dependent increase in the BBB permeability $K_{\text{trans}}$ constant in the entire hippocampus, its CA1 region and dentate gyrus, but not CA3 region. Single data points for the $K_{\text{trans}}$ constant from 17 individuals with no cognitive impairment

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**BBB breakdown in the hippocampus in the living human brain during normal aging (Neuron 2015)**

Fig. S2. Correlation between albumin cerebrospinal fluid to plasma quotient (Qab) and the blood-brain barrier $K_{\text{trans}}$ values in the hippocampus and its subfields during normal aging and aging associated with mild cognitive impairment (related to Figure 2A). (A) An increase in $Q_{\text{ab}}$, in individuals with mild cognitive impairment (NCI, n=17) compared to age-matched individuals with no cognitive impairment (NCI, older; n=14). Boxplots represent the median
Brain Trauma CT perfusion

- Seventy-six patients were included. In patients with a decreased Glasgow Coma Scale score
- In the acute phase of mild head injury, disturbed cerebral perfusion is seen in patients with normal noncontrast CT correlating with severity of injury and outcome

Metting Z et al. Perfusion computed tomography in the acute phase of mild head injury: Regional dysfunction and prognostic value, Annals of Neurology June 2009 Pages 809 - 816

Exercise Plays a Preventive Role Against AD?

- Wuu J, Hase K, Kinjo J, Manzon JE, et al. Physical activity, including walking, and cognitive function in older women. JAMA 2003; 290:1454-1453. This is the largest cross-sectional study to date. It confirmed the association between physical activity and cognitive decline.

Radak et al. JAD Volume 20, Number 1 / 2010

Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial

- OBJECTIVE: To determine whether physical activity reduces the rate of cognitive decline among older adults at risk
- CONCLUSIONS: In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period

Lautenschlager NT. JAMA. 2009 Jan 21;301(3):276
CSF flow approximately doubles during sleep.

**Sleep Apnea and AD**

Obstructive sleep apnea and cognitive impairment in the elderly


Human GD Deposition in Perivascular Spaces

X-ray microanalysis revealed gadolinium predominantly in large foci within the endothelial wall.

18-42% had crossed the blood-brain barrier and was deposited into the neural tissue interstitium.

TEM micrograph and X-ray spectrum showing the presence of gadolinium in electron-dense foci in a gadodiamide-exposed patient.

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Glymphatic dysfunction: AD

Is this related to decreased perfusion?

- Dysfunction of this clearance system likely important in many neurodegenerative diseases (accumulation of proteins)
- AD characterized by accumulation of proteins (amyloid, tau)
  - Found that beta-amyloid is cleared by glymphatic system along paravenous pathway
    - Injection of fluorescent or radiolabeled amyloid into mouse striatum
      - AQP4 knockout mice 60% reduction in CSF fluid flux through parenchyma
      - 55% reduced clearance of labeled beta amyloid
- Beta amyloid accumulation in PVS of penetrating arteries

Glymphatic dysfunction: TBI

- TBI induces accumulation of beta amyloid peptide and C tau
- C-tau correlates with severity of TBI: biomarker
- Hypothesized that increased interstitial tau may lead to cellular uptake and fibrillary aggregation
- Formation of large astroglial scars and persistent activation of innate inflammation
- Loss of polarization (AQP4 from foot to parenchymal processes like aging)
- Iliff et al. showed that tau accumulates around large veins and amount remaining in tissue correlates with decrease in glymphatic clearance → suggests glymphatic removal of tau important in limiting secondary neuronal damage following TBI

Glymphatic dysfunction: TBI & AD

- Post traumatic impairment of the glymphatic pathway promotes tau aggregation
- Loss of perivascular AQP4 polarization after TBI impairs paravascular clearance of interstitial solutes including tau
- Promotes accumulation of phosphorylated tau → neurodegeneration, persistent inflammation → cognitive dysfunction

A mechanism for degeneration of aging neuronal membranes that leads to abnormal amyloid precursor protein processing and Alzheimer’s disease

Investigators: Michael G. Harrington, MB, CHB, FRCP, Program Director, Molecular Neurology Department, HMRI, 89 N. El Molina Avenue, Pasadena, CA, 91101
mg@hmr.com/ (626) 795-4434 ext 218
Co-Investigators: A.N. Fontham (HMRI), Katie Canio (HMRI), Helena Choi, Carol Miller.

ADRC sponsor: Helena Choi

Brain-derived membrane nanoparticles in cerebrospinal fluid (CSF) have oxidized lipids in AD and as early as preclinical AD. To further test this hypothesis, we propose to compare membrane morphology and biochemistry in CSF and brain subcellular fractions from USC ADRC to test if CSF findings replicate in brain. Success of this project should enable a strong independent NIH funding proposal.

Specific Aims

1) Measure fatty acid, sphingolipid, phospholipid, APP and β-amyloid concentrations in nanoparticles from CSF, and in plasma membrane/mitochondrial/synaptic sucrose preparations from the same cognitively healthy control (n = 5) and AD (n = 5) brains.
2) Measure the thicknesses of CSF nanoparticles and brain subcellular membranes.
3) Determine whether the changes in Aims 1 & 2 are similar in brain and CSF; if they support an early mechanism for APP distribution and the redox post-mitotic hypothesis.
Shunting for dementia?

Assessment of low-flow CSF drainage as a treatment for AD
Results of a randomized pilot study

Abnormal CSF flow
• Implicated in the etiology of Normal pressure hydrocephalus, Vascular dementia, Alzheimer’s disease, intracranial hypertension
• Vascular disease (one potential cause of abnormal CSF flow) results in a decrease in cerebral arterial compliance
• Hydrocephalus (another cause) results in abnormal pressure gradients and changes brain compliance

Glymphatic dysfunction: Stroke

Gabel et al (Stroke 2014) suggest glymphatic system impaired after acute embolic stroke, SAH

Glymphatic function restored after spontaneous arterial recanalization
Ventricular injection of IPA improved glymphatic perfusion after SAH
Glymphatic dysfunction after acute stroke may prevent adequate clearance of excitatory neurotransmitters and promote neuronal death
This potentially reversible dysfunction may result from: decrease in arterial pulsation because of vessel occlusion or occlusion of perivascular space by extrinsic compression

NPH
• Loss of brain elasticity results in arterial pressure transmitted to the incompressible CSF in ventricles
• Imaging findings:
  • Ventriculomegaly out of proportion to subarachnoid space
  • Prominent periventricular halo
  • Hyperdynamic flow through aqueduct
    • CSF flow void in the cerebral aqueduct
    • Elevated velocity on Phase contrast MRI

Abnormal CSF flow
• Implicated in the etiology of Normal pressure hydrocephalus, Alzheimer’s disease, late-onset depression, intracranial hypertension, NPH, leukoaraiosis.
• Vascular disease (one potential cause of abnormal CSF flow) results in a decrease in cerebral arterial compliance.
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  • Metabolic Waste Clearance
  • Peripheral Immune Surveillance
  • Cell trafficking Pathway
  • Route for Signaling Molecule Distribution

Role of CSF
**Time-SLIP Technique**

- 15 different TI values at 200msec intervals starting at 2000msec
- Total acquisition time = 3.5 minutes depending on the pulse rate

**Scan setup: Tag placement**

- Normal reflux from 3rd to lateral ventricles

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**Tag placement**

- The top of the tag is placed at the inferior margin of the septum pellucidum

**Measurements from the upper margin of the tag vs. inferior margin of septum pellucidum to the upper point of reflux**

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**Tag placement matters**

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**NPH**

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  - Hyperdynamic flow
Patient 1 with NPH Responded to shunting

Patient 2 with NPH Responded to shunting

Patient 2 with NPH Responded to shunting

Patient 2 with NPH Responded to shunting

Patient 2 with NPH Responded to shunting

Aliasing artifact at the cerebral aqueduct because the venc is set too low

Parkinson’s Disease
Reflux of CSF into Lateral Ventricles in patients with memory complaints

Study to evaluate CSF reflux with dementia (51 patients so far)

Grading the amount of reflux

Variation in Reflux Grade

Marker of brain compliance Perfusion, CSF flow, BBB

- Many degenerative diseases involve an inflammatory & vascular component along with changes in brain compliance.
- Altered CSF flow reducing the clearance of toxic proteins such as beta amyloid.
- Effect of CSF flow, glymphatic drainage
- Related to perfusion and venous clearance

10 Strategies (some surprises)

1. Coffee: caffeine, anti-oxidant effects, stimulant
2. Floss & periodontal disease, inflammation
3. Googling and Internet searching
4. Aerobic exercise 30 mins a day
5. Apple a day or apple juice – acetylcholine
6. Prevent head blows
7. Meditation & Sleep: improved blood flow/glymphatics
8. Vitamins, esp. Vitamin D. Menopause & HRT?
9. Mental Stimulation: play music instrument, language
10. Avoid infections cold sores, gastric ulcers, Lyme disease, pneumonia and the flu

Jean Carper's newest book: "100 Simple Things You Can Do to Prevent Alzheimer's"
Summary

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  - Arterial Pulsatility, CSF – ISF Gradients
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Effect of Mindfulness and Neural Plasticity

Real Time Imaging
Auto Tracing (Dynatracer)

Deep Inspiration

Cardiac pulse

15 msec/image: sequential acquisition

n=22 | n=22
n=27 | n=27
n=30 | n=30
n=30 | n=30
n=50 | n=50

Luders et al. (2000) Neurology
Luders et al. (2001) Neurology
Luders et al. (2001) Human Brain Mapping
Luders et al. (2002) Neurology
Luders et al. (2002) Front. Human Neuroscience