Blood Brain Barrier in Delirium

U13 Delirium Conference

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  – None
Outline

• Blood brain barrier physiology and pathophysiology in acute illness
• Astrocyte damage and delirium
• Endothelial dysfunction and delirium
• Limitations
• Future directions
BBB and Brain Parenchyma

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Blood Brain Barrier Function

• Protects the brain through selective permeability
  – When damaged, allows inappropriate passage of molecules from the plasma into the CNS and from the CNS into the plasma
  – Biomarkers of neurologic injury in the plasma may result from direct damage to the BBB or from direct neuronal damage leading increased diffusion through the BBB
Altered BBB Permeability

- In vitro studies have shown IL-1β and VEGF-A increase BBB permeability
- VEGF increases BBB permeability after ischemia in rats
- Circulating TNF-α increased BBB permeability in mouse model of *E coli* and *Strep pneumo* sepsis
- Permeability changes in multiple rat sepsis models
- Procalcitonin, IL-8, and CRP have been associated with acute brain dysfunction in critically ill patients
  - Via BBB permeability?

Argaw A et al. *J Immunol.* 2006; 177: 5574-84
BBB Permeability with Increasing Age

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Brain’s Response

• Production of cytokines, cell infiltration, and tissue damage
• Altered patterns of neuronal activity by modulating synthesis of neurotransmitters and changing expression of neurotransmitter receptors
  – Clinical symptom = delirium?

Mostly based on animal and autopsy data

Signalling in Pathological Conditions

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Astrocyte Injury

- S100B is expressed and secreted by astrocytes after CNS injury/ischemia and cell death
  - Plasma S100B validated as a measure of BBB injury against CSF-serum albumin ratios and MRI
  - Correlate with endothelial cell structural changes in cortical biopsy specimens
  - Plasma levels increases in brain trauma, ischemia, toxic injury, and neurodegenerative diseases
  - Exact function unknown, may be involved in neuronal and glial growth, proliferation, and activation
  - Values may differ depending on the assay used

Cata JP et al. BJA. 2011; 107: 844-58
S100B and Elderly

• Levels correlated with delirium (CAM) in 120 elderly hip fracture patients
  – Highest levels during delirium, but before and after were also higher than non-delirious patients

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S100B and Septic Encephalopathy

- 170 patients with severe sepsis or septic shock
- S100B and NSE measured daily x 4 days
- Encephalopathy determined by ICU physician
- Elevated levels of S100B were associated with low consciousness (coma, stupor, somnolence) encephalopathy (p=0.004), brain lesions, and mortality (p=0.04)
- NSE failed to predict outcome

Our Studies

Neurologic Injury
- Blood Brain Barrier
- Brain Parenchyma

Endothelial Dysfunction
- Vascular Reactivity
- Endothelial Activation

Acute Brain Dysfunction (CAM-ICU, RASS)

Long-term Cognitive Impairment (RBANS, Trails B)
S100B and Delirium

• Prospective cohort of 134 patients in shock or respiratory failure
• Median age 57 years, median APACHE II of 26 with 2 days of severe sepsis
• Median ICU LOS of 5 days
• Measured S100B at enrollment
• Daily RASS and CAM-ICU assessments
• Manuscript with results pending
Endothelial Dysfunction Hypothesis

- Impaired perfusion
- Altered permeability
- Toxin exposure
- Neuronal injury

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Endothelium Pathophysiology

• Upregulation of inducible nitric oxide synthase and superoxide production in brains of septic mice
• Hypoxia leads to activation of protein kinase C and BBB endothelial cell permeability changes via tight junction protein phosphorylation
• E-selectin associated with BBB leukocyte adhesion and BBB dysfunction in septic mice
• Structural and functional alterations of BBB endothelial cells associated with microvascular permeability and impaired microcirculation

Yokoo H et al. *PLOS One*. 2012; 7: e51539
Vachharajani V et al. *Obesity*. 2011; 20: 498-504
Endothelial Dysfunction Study

- Prospective cohort of 134 patients in shock or respiratory failure
- Median age 57 years, median APACHE II of 26 with 2 days of severe sepsis and 5-day ICU stay
- Measured endothelial vascular reactivity with peripheral artery tonometry at enrollment
- Daily RASS and CAM-ICU assessments
Vasc Reactivity vs. DCFDs

\[ P = 0.02 \]

Vasc Reactivity vs. Delirium Duration

Endothelial Activation

• Measured endothelial activation with PAI-1, E-selectin, Ang-2 at enrollment of previously described cohort
• Manuscript with results pending
Mediation

• Adjustment for BBB injury in systemic endothelial dysfunction models to assess if BBB injury mediates association between endothelial vascular reactivity and activation with acute brain dysfunction
• Manuscript with results pending
Endothelial Modulation and Brain Dysfunction

- Physical therapy (PT) has been shown to improve endothelial function in outpatients and reduce delirium duration in ICU patients.

- Hypotheses:
  - Improvement in endothelial function over time is associated with less brain dysfunction in ICU patients.
  - Early PT is associated with improvement in endothelial function in ICU patients.
ACT Endo Function Study

- Prospective cohort study of 72 patients nested within a RCT of early PT versus usual care in adult medical and surgical ICU patients with shock or respiratory failure
- Endothelial vascular reactivity was assessed at enrollment and at 7 days or hospital discharge via peripheral artery tonometry
- Daily RASS and CAM-ICU assessments
- Manuscript with results pending
Limitations

• Functional assessment of the BBB is limited by anatomical characteristics and current technology
  – MRI: complicated scanning protocols, including dynamic contrast enhanced MRI, long scanning sessions, difficult algorithms

• CSF to serum albumin quotient to determine BBB permeability is invasive and impractical
  – Elevated in elderly at baseline
  – Necessitates use of plasma biomarkers

• Transcranial doppler and near-infrared spectroscopy
  – Large vessels and superficial structures
  – Microdialysis assessment invasive
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Necessitates use of surrogate markers
Future Assessment

• “Post-pre” and “linear dynamic” methods with MRI
  – Semi-quantitative permeability assessment
  – Localization of dysfunctional BBB
  – Partial dynamic imaging protocol with easier to apply algorithms

• Surrogate markers
  – Is there a better indicator of BBB function?
  – Does systemic endothelial dysfunction = cerebral endothelial dysfunction?
Therapeutic Options for BBB

- Improved BBB disruption in animal models of sepsis, neoplasm, and seizure

Heme oxygenase-1  Steroids
Magnesium         Calcium channel blockers
Immunoglobulins   Free radical scavenging
Anti-epileptics   ARBs

Gurses C et al. *Brain Res.* 2009; 1281: 71-83
Gurses C et al. *Brain Res.* 2013; 1494: 91-100
Cucullo L et al. *Brain Res*. 2004; 997: 147-51
Yokoo H et al. *PLOS One*. 2012; 7: e51539
Therapeutic Options for BBB

• Early Mobility
  – Serial measurements of S100B, endothelial vascular reactivity, endothelial activation in larger mobility cohorts with delirium monitoring

• Statin Pharmacotherapy
  – Known modifiers of the endothelium and reduce inflammation
  – May be protective of delirium
  – Measure S100B, endothelial vascular reactivity, and endothelial activation in upcoming RCTs of statin vs. placebo
Key Points

• Both BBB injury and endothelial dysfunction are independently associated with acute brain dysfunction during critical illness

• BBB injury does not appear to mediate the effects of endothelial dysfunction on acute brain dysfunction
  – Perfusion, autoregulation, and permeability separate with regards to delirium?

• Many potential routes of future investigation, including therapeutic trials, high-risk populations, long-term outcomes
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Questions?