Delayed neurological health risks from acute brain injury

Lessons from neurotrauma and iatrogenic brain injury.

Statement of Problem

- **During extended manned space missions, HZE particles and protons will traverse the brain, producing acute damage.**
- **Will this acute damage trigger delayed neurological and/or neurobehavioral deficits?**

Approach

- **What is know about the risk for developing delayed neurological /neurobehavioral deficits following acute brain injury from neurotrauma or iatrogenic brain injury cause?**

Traumatic brain injury

- **2 million people each year sustain head injuries. TBI results in 150,000 hospital admissions per year**
- **Patients with mild TBI exhibit immediate and persistent neurocognitive deficits.**

Mechanisms contributing to traumatic brain injury

- **Moderate/Severe TBI**
  - **Vascular damage**
  - **Hypoxia**
  - **Edema**
  - **Diffuse axonal injury (irreversible structural damage)**
  - **Secondary vasospasm**
  - **Secondary injury (cell mediated, free radical mediated)**
- **Mild TBI**
  - **Diffuse axonal injury (reversible structural damage)**

Iatrogenic CNS injury

- **Neurosurgical procedures**
- **Radiation therapy**
- **Obstetric procedures**
- **Surgical procedures, cardiopulmonary bypass**

Cardiopulmonary Bypass

- **400,000 cases per year**
- **High incidence of neurological complication**
- **Brain injury accounts for 20% of CPB surgical mortality**
- **Significant risk of post-surgical neurocognitive deficits similar to those observed in early stages of Alzheimer Disease**

Neurocognitive deficits following bypass procedure

- **Cognitive impairment have been reported to occur in up to 70% of bypass patient at discharge**
- **Persistent neurocognitive deficits have been reported in 20 to 30% of patients for at least 12 months post-operation**

Mechanisms contributing to mild CPB brain injury

- **Air emboli**
- **Particulate emboli (from pump tubing)**
- **Cerebral hypoperfusion**
- **Anesthetic effects Inflammatory mediators (TNF, IL)**
- **Secondary injury (cell mediated, oxidative stress, excitotoxicity)**

Questions

- **Are there risk factors that affect response to mild brain injury?**
- **Does acute traumatic or iatrogenic brain injury increase the risk of developing later neurological disease?**

Lesson 1: Patients exhibit different propensities for developing deficits

- **Factors affecting likelihood of developing neurological / neurobehavioral deficits following CBP and TBI**
  - **Age**
  - **Years of Education**
  - **Physiological status**
  - **Pre-existing psychiatric disorder**

NASA Relevance

Good news…Assuming common mechanisms contribute to CNS damage by radiation / CBP / TBI, astronauts have reduced risk for developing neurological/cognitive deficits

Lesson 2: Genes determine how the brain will respond to injury

- **Apolipoprotein E genotype affects likelihood of developing neurological and/or neurobehavioral deficits**
  - **There are three isoforms of ApoE expressed in humans, designated ApoE2, ApoE3, and ApoE4**
  - **ApoE4 gene frequency in US is 15%**
  - **ApoE4 shown to be risk factor for spontaneous, late onset Alzheimer Disease**
  - **Individual with ApoE4 gene also at greater risk for developing more neurological and neurocognitive deficits following brain injury following CPB and TBI (and stroke, fetal iodine deficiency syndrome)**

NASA Relevance

Bad news…One in four astronauts likely inherited the ApoE4 genes and may be genetically predisposed to CNS injury

Lesson 3: Acute brain injury can trigger delayed neurological neurobehavioral deficits

- **Numerous studies have reported the association between a history of mild head injury and risk of developing spontaneous, late onset Alzheimer disease**
- **Alzheimer disease patients with history of mild head injury develop the disease at an earlier age. (Nemetz et al, Am J Epidemiology 1999)**

Lesson 3: Acute brain injury can trigger delayed neurological neurobehavioral deficits

- **Five year follow-up on neurocognitive status of cardiopulmonary bypass patients reported that many of the patients with transient, peri-operative cognitive deficits exhibit a second, delayed deterioration of mental status. (Newman et al. in press, Dec 2000 NEJM)**
- **Traumatic brain injury elevates the Alzheimer's amyloid peptide A beta 42 in human CSF. (Emmerling et al. Annal NY Acad Sci 2000)**

Basis for delayed neurological effects following mild injury

- **Chronic oxidative stress**
- **Amyloidogenesis. (Increased synthesis of beta amyloid precursor, production fibrillogenic amyloid beta-peptide derivative.)**

Experimental Questions for NASA Risk Assessment Efforts

- **Does exposure to HZE and proton radiation lead to chronic CNS oxidative stress and/or amyloidogenesis?**
- **Are the magnitude of these stresses sufficient to trigger and/or aggravate later neurological disease?**
- **Does ApoE genotype affect response to HZE and proton radiation.**

Summary

- **In light of evidence derived from studies of mild traumatic and iatrogenic brain injuries, efforts should be directed to assessing the long term neurological effects caused by acute low level particle radiation exposure to determine the risk that**
  - **Acute radiation injury wil increase the likelihood of developing later neurological disease**
  - **Acute radiation injury will lower the age of onset of dementia**
  - **Acute radiation injury will affect the progression of neuropathologic and functional changes attending later neurodegenerative disease**