Outcome of Head Trauma in Children

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Introduction

- Pediatric traumatic brain injury (TBI) is the leading cause of death in children over 1 year of age.
- Significant disability is frequent with negative impacts on functional long-term outcome even when the initial injury is mild.

Epidemiology

- TBI should be considered in all injured children, particularly those with:
  - Suspicious mechanism of injury.
  - Loss of consciousness.
  - Multiple episodes of emesis.
  - Intubated patients.
  - Multiple trauma.
- Blunt trauma due to MVA is the commonest mechanism of TBI.
- In children of less than 4 years of age, 30–50% of TBI is caused either by falls or inflicted TBI (iTBI).

Epidemiology

- Ten percent of TBI is severe with an associated mortality rate of 50%.
- After TBI:
  - Mortality is lower in children compared with adults (10.4 vs. 2.5%).
  - Secondary insults can worsen outcome, such as:
    - Hypoxia ($PaCO_2$ <60mmHg),
    - Hyperglycemia (glucose >200mg/dl),
    - Hyperthermia (temperature >38.0 C),
    - Hypotension (SBP <5th percentile for age).
    - Intracranial hypertension (ICP >20mmHg)

Patterns of Injury

- Children are more susceptible to TBI because:
  - Have a larger head to body size ratio.
  - Thinner cranial bones providing less protection to the intracranial contents.
  - Less myelinated neural tissue that makes them more vulnerable to **damage** and a greater incidence of **diffuse injury** and **cerebral edema** compared with adults.

Patterns of Injury

- Children have a higher incidence of increased ICP following TBI than adults (80 vs. 50%).

- Diffuse TBI is the most common type of injury and results in a range of injury severity from concussion to diffuse axonal injury (DAI).

Patterns of Injury

- The diagnosis of TBI during the acute care management is primarily made by computed tomography (CT) of the brain.

- Early post injury MRI is the preferred method for diagnosis of DAI because CT scan has a low sensitivity to diagnose DAI.

- Repeated neuroimaging often shows secondary injury due to cerebral edema and TBI progression.

Physiology and pathophysiology

- Age and sex differences in children must be considered when examining changes after pediatric TBI.

Cerebral Metabolic Rate

- Global cerebral metabolic rate (CMR) for oxygen and glucose is higher in children than in adults:
  - oxygen 5.8 vs. 3.5ml/100 g brain tissue/min
  - glucose 6.8 vs. 5.5ml/100 g brain tissue/min

Cerebral Blood Flow

- Cerebral blood flow (CBF) changes with age and may be higher in girls compared with boys.

Cerebral Autoregulation

- Following TBI, CBF and cerebral metabolic rate of oxygen (CMRO2) may not be matched, resulting in either cerebral ischemia or hyperemia.
  - Incidence of cerebral hyperemia is only between 6 and 10%.
  - Incidence of CMRO2 may be normal, low, or high.

Cerebral Autoregulation

- Lower limit of autoregulation (LLA) is the same for younger and older children (46–76mmHg).

- As blood pressure (BP) increases with age, young children may be at increased risk of cerebral ischemia due to lower BP reserve [mean arterial pressure (MAP)LLA].

Cerebral Autoregulation

- Similar to adults, the incidence of impaired cerebral autoregulation is higher following severe (42%) compared with mild TBI (17%)

- Children with impaired cerebral autoregulation early after TBI may have poor long-term outcome because hypotension is common after pediatric TBI and may lead to cerebral ischemia.

Inflicted Traumatic Brain Injury

- Most inflicted injury deaths involve TBI.
- Children with iTBI commonly present with:
  - Altered consciousness
  - Coma
  - Seizures
  - Vomiting
  - Irritability
  - Histories are often lacking and injuries may be out of proportion to history or developmental milestones.

Inflicted Traumatic Brain Injury

- Types of injuries include:
  - Subdural hematoma
  - Subarachnoid hemorrhage
  - Skull fractures
  - DAI with or without cerebral edema.

- Outcome after iTBI is typically poor.

TBI Biomarkers

- Misdiagnosis and delayed recognition of TBI can frequently delay care and worsen outcome especially in situations in which the history is often missing or inaccurate.

- Commonly used diagnostic tools such as physical examination, Glasgow Coma Scale (GCS) score, and CT do not differentiate between iTBI and accidental TBI.

- Select biomarkers may be able to aid with early recognition and prognosis after TBI.

TBI Biomarkers

- The use of Biomarkers as diagnostic and prognostic tools has been an area of clinical interest and research over the past 30 years.

- Pediatric specific research has been limited due to multi-faceted reasons:
  - The high morbidity and mortality associated with Pediatric TBI
  - The age related wide variation of sensitivity and/or specificity of many biomarkers.

TBI Biomarkers

- A wide range of biomarkers have been identified:
  - S100B
  - Neuronal-Specific Enolase (NSE)
  - Myelin Basic Protein
  - Vascular Cell Adhesion Molecule
  - Interleukin (IL)-6
  - Intracellular Adhesion Molecule
  - IL-12
  - Eotaxin
  - Tumor Necrosis Factor Receptor 2
  - Matrix Metallopeptidase 9
  - Hepatocyte Growth Factor
  - Fibrinogen
  - Nerve Growth Factor (NGF)
  - Doublecortin Expression (DCX)

- Multiplex bead technology can simultaneously assess multiple biomarkers and requires small volumes of blood for analysis.

TBI Biomarkers

- Peak serum neuronal-specific enolase (NSE) and more delay of time to peak serum concentration of NSE, S100B, and myelin basic protein are reported in children with poor functional and cognitive outcome in iTBI.

  » Beers SR, Berger RP, Adelson PD. Neurocognitive outcome and serum biomarkers in inflicted versus noninflicted traumatic brain injury in young children. J Neurotrauma 2007; 24:97–105.

TBI Biomarkers

- Higher serum NSE has also been associated with GCS of 8 or less and increased risk of death.

Guzel A, Er U, Tatli M, et al. Serum neuron-specific enolase as a predictor of short-term outcome and its correlation with Glasgow Coma Scale in traumatic brain injury. Neurosurg Rev 2008; 31:439–444.

TBI Biomarkers

- Higher serum S100B levels at 24 h in patients with severe TBI are associated with death or unfavorable 3-month outcomes.
  - » Rainey T, Lesko M, Sacho R, et al. Predicting outcome after severe traumatic brain injury using the serum S100B biomarker: results using a single (24 h) time-point. Resuscitation 2009; 80:341–345.

TBI Biomarkers

- Early high cerebrospinal fluid (CSF) nerve growth factor (NGF), IL-6, and doublecortin expression (DCX) concentrations at 2 h after TBI, and high NGF, DCX, and NSE concentrations at 2 h after admission within 4 h after TBI are associated with greater TBI severity.
- NGF, IL-6, and DCX upregulation between 2 and 48 h after TBI and NGF, and DCX upregulation with lower NSE expression between 2 and 48 h after admission are associated with good neurological outcomes, reflecting endogenous attempts at neuroprotection in response to TBI.
    - » Chiaretti A, Antonelli A, Mastrangelo A, et al. Interleukin-6 and nerve growth factor upregulation correlates with improved outcome in children with severe traumatic brain injury. J Neurotrauma 2008; 25:225–234.
    - » Chiaretti A, Antonelli A, Genovese O, et al. Nerve growth factor and doublecortin expression correlates with improved outcome in children with severe traumatic brain injury. J Trauma 2008; 65:80–85.
    - » Chiaretti A, Barone G, Riccardi R, et al. NGF, DCX, and NSE upregulation correlates with severity and outcome of head trauma in children. Neurology 2009; 72:609–616.

Characteristics of Serum Biomarkers

Biomarkers	Abbreviation	Function	Source
Neuron-specific enolase	NSE	Increasing neuronal chloride levels during onset of neural activity	Cytoplasm of neurons, platelets, and pRBCs
Calcium-binding protein	S100B	Low-affinity calcium-binding protein, inhibit synaptic plasticity by binding to neuronal receptors	Cytosol of astroglial cells, bone marrow, fat and skeletal muscle
Myelin basic protein	MBP	Abundant protein in myelin	Myelin
Interleukin-6	IL-6	Stimulates immune response to trauma, tissue damage, and inflammation	T cells, macrophages, vascular smooth muscle cell, and osteoblast
Nerve growth factor	NGF	Maintenance of sympathetic and sensory neurons, protective	Astrocytes, microglia, immature Schwann cells, satellite cells, skin, vascular, and other smooth muscle cells, endocrine tissues, and exocrine salivary
Doublecortin expression	DCX	Expressed in neuronal precursors; hippocampus, subventricular zone, temporal cortex, protective	Microtubule-associated protein

pRBCs, packed red blood cells.

- Chiaretti A, Antonelli A, Mastrangelo A, et al. Interleukin-6 and nerve growth factor upregulation correlates with improved outcome in children with severe traumatic brain injury. J Neurotrauma 2008; 25:225–234.
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- Although many general principles of managing pediatric TBI are similar to adults, there are unique anatomic, physiological, and pathophysiological features of children with TBI worth recognizing and considering as a part of the care of these injured children.

THANK YOU