Global Ischemia Associated with Anoxic Brain Injury:
Neuro, Movement, and Cognitive Sequelae
Gary Galang, MD

The Neurological Complications Associated with Global Ischemia

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The 6e Experience

- N=8, 6M/2F average age of 30 yo.
- 3 IVDA, 1 asphyxiation, 4 cardiac arrest (1 from intoxication)
- 8/8 had arousal/cog deficits (5/8 were vegetative)
- 6/8 had PSH
- 6/8 had spasticity
- 6/8 had movement disorders

Whyte et al

- 181 Rehabilitation Patients
  - Hypertonic/spasticity (8.3%)
  - UTI (6.4%)
  - Agitation/aggression (6.4%)
  - Sleep disturbance (6.2%)
  - Hyperkinesia/motor restlessness (4.7%)
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Anoxic Brain Injury: Pathophysiology

Etiology: "Global Ischemia" from Cardiac Arrest, Shock, Asphyxia,
Global ischemia: Diminution of cerebral blood flow which results in a pattern (selective ischemic necrosis)
- Normal CBF: 50-75 ml/100 g of tissue/ min
- Ischemic depolarization: 18 ml/100 g of tissue/ min
- Cell death: 10 ml/100 g of tissue/ min

Ischemic Core vs Ischemic penumbra
Reperfusion injury from influx of neutrophils and reactive Oxygen Species

Global Ischemia: Determining factors

• Anoxic Vulnerability
  – Cortical Watershed areas, CA-1 area of hippocampus, and cerebellar Purkinje cells are vulnerable
  – Subcortical Areas (brainstem, thalamus and hypothalamus) are more resistant

• Injury factors

Anoxic Brain Injury: Pathophysiology

• Necrosis vs Apoptosis, regulated vs Programmed
• Necrosis: exposure to Excitatory neurotransmitters, mitochondrial failure, cell wall compromise, edema and lysis
• Apoptosis: Mitochondrial dependent intrinsic pathway and receptor mediated extrinsic pathway
• Although distinct, presented as a spectrum of processes that coexist in injured tissue
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**Glutamate release**

- **Mg²⁺, Zn²⁺, glycine, PCP** (receptor antagonists)

- **Ca²⁺**

- **Na⁺/K⁺ pumps**

- **ATP**

**Secondary Injury after TBI**

**Neuronal death**

**Excitotoxicity: Notes**

- Glutamate: Most abundant EAA, has limited reuptake causing binding with NMDA and Ca influx
- Induction, Amplification, and Expression = Cell death
- NO: Mixed effects (increased CBF vs Cytotoxic effects)
- Dopamine and Norepinephrine efflux can propagate the injury
  - Blockade seems to have a neuroprotective effect
  - Exposure increases striatal nerve cell vulnerability
  - Byproducts (hydrogen Peroxide, superoxide, hydrogen radicals) are toxic as well

**Excitotoxicity and cell death: Continuation**

- Inflammation
  - Migration of peripheral leucocytes into the brain
  - Release of inflammatory cytokines (IL-1 and TNF –A) which compromises BBB
- Glycemic Control
  - Poor glycemic control = release of EAA’s, massive neutrophil influx, mitochondrial damage
- Temperature (30-34 deg C)
  - Mitigation of excitotoxic processes, increased membrane stability, decreased brain metabolic requirements
Arousal

- AROUSAL: The intensity of sensory stimulation required to interrupt sleep and the duration of the response following the stimulation
  - TONIC: Fluctuations in the degree of wakefulness that occur in a diurnal basis
  - PHASIC: Rapid fluctuations in wakefulness that occur in response to warning signals or unexpected stimuli
  - VIGILANCE: The capacity to sustain the orienting reaction through time

CONSCIOUSNESS

- wakefulness
- the ability to detect and perceptually encode interoceptive and exteroceptive stimuli
- capacity to formulate goal-oriented behavior
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Reticular Formation: “neurophysiologic seat of consciousness”

- poorly differentiated area of the brain stem, centered roughly in the pons. The reticular formation is the core of the brainstem running through the mid-brain, pons and medulla.
- The ascending reticular activating system connects to areas in the thalamus, hypothalamus, and cortex, while the descending reticular activating system connects to the cerebellum and sensory nerves.
- Caudal lesions cause insomnia vs. rostral lesions cause hypersomnia.

COMA

- State of un-arousable unresponsiveness in which there is no evidence of self or environmental awareness
- Absence of sleep wake cycles on EEG
- No evidence of purposeful or spontaneous movement, discrete localizing responses, or language comprehension or expression.
- Indicates failure of the RAS and the cortex
  - Severe bi-hemispheric cortical or white matter injury
  - Focal brainstem lesion of the rostral RAS

VEGETATIVE STATE: AAN

- No awareness of self and environment
- No evidence of sustained, reproducible, purposeful or voluntary responses
- No evidence of language comprehension or expression
- Intermittent wakefulness manifested by the presence of sleep wake cycles
- Preservation of autonomic function to permit survival with medical and nursing care
- Bowel/ bladder incontinence
- Variably preserved cranial nerve and spinal reflexes
Minimally Conscious: AAN

- Following simple commands
- Gestural or verbal yes/no responses (regardless of accuracy)
- Intelligible verbalization
- Purposeful behavior, including movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not due to reflexive activity.

Why distinguish VS from MCS???

- Improve diagnostic accuracy distinguishing VS from other conditions
- More accurate prognosis in patients with impaired consciousness
- Necessary to define patient groups for replication and comparison in research

PREVALENCE OF MCS (Strauss et al. 2000)

- Pediatric database California
- N=5,075 with severe disorders of consciousness
  - 89% MCS
  - 11% VS
- Estimated prevalence in MCS in US: 112,000-280,000
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Criteria for Emergence from Minimally Conscious State to the Confused States

- Functional interactive communication: Accurate yes/no responses to 6/6 basic situational orientation questions on 2 consecutive evaluations.
- Functional object use: general appropriate use of at least 2 different objects on 2 consecutive evaluations.

*Complicated by Aphasia and Apraxia

Emergence: Acute Confusional State (ACS)

- Temporal and Spatial Disorientation
- Distractibility
- Anterograde Amnesia
- Impaired Judgment
- Perceptual Disturbances
- Restlessness and akathisia
- Sleep Wake Disturbances
- Emotional Lability

Prognosis: Early Predictors

- Poor outcomes (Death, Vegetative or severely disabled) with:
  - Myoclonus with 24-48 hours
  - Bilateral Absence of Short – latency SSEP N20 Wave at 24-72 hours
  - (·)EEG Activity > 20-21uV at 72 hours
  - Absence of pupillary responses > 72 hours

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PROGNOSIS: Sub Acute to Chronic

- Persistent at 1 month, Permanent at 3 months
- The longer the duration of the vegetative state, the worse the outcomes
- >40 yo have a smaller chance of recovery
- Ventilatory dysfunction, lack of early motor reactivity, late onset epilepsy, and hydrocephalus indicate a poorer prognosis.

REGAINING CONSCIOUSNESS

- TBI (N: 434)
  - 3 months: 33% regained consciousness, 67% dead or VS
  - 6 months: 42%
  - 12 months: 52%
  - >12 months 7/434
- NON TBI: (N: 169)
  - 85% dead within 1st month
  - 3 months: 11% have regained consciousness
  - 6 months: only 2 more regained consciousness
  - 1yr, 15% regained consciousness, 32% PVS, 53% dead

SURVIVAL

- Average life expectancy is 2-5 years
- In 1 year, 33% of traumatics and 53% of non-traumatics have died
- 82% mortality in 3 years, 95% in 5 years
- Causes of mortality
  - Infection (pulmonary, UTI): 52%
  - Multi organ system failure: 30%
  - Unknown: 9%
  - Respiratory failure: 6%
  - Strokes/tumors: 3%
- Young to middle aged adults did better than infants and the elderly

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DOC: Pharmacologic Interventions
- Amantadine
  - Giacino, White, et al administered amantadine (200-400 mg) to Vs and MCS patients 4 – 16 weeks post injury for 4 weeks with 2 week washout
  - Significant recovery (following commands, yes no accuracy, speech intelligibility, functional object use) in amantadine group w/c maintained after Tx
  - 18% remained vegetative in amantadine group vs 31% in placebo

DOC: Pharmacologic Interventions
- Zolpidem (Ambien): a selective GABA 1 agonist
  - At 10 mg doses, paradoxical improvements in arousal (emergence from VS) Command following, visual pursuit, and automatic social greetings in 1/14 patients
  - Other studies reflect a positive response in 5-7% of patients (traumatic and atraumatic BI)

DOC: DBS
- Central Thalamic DBS (C-TDBS): electrical impulses sent to targeted nuclei within the central thalamus that control arousal, sustained attention, working memory and motor intention.
  - Schiff et al. Initial case of 36 yo M in MCS for 6 years sp CT-DBS on 30 day on/off cycle showed increased arousal and functional improvements during the on cycle
  - Theory: Activation of cortical networks that have been down regulated from mesodiencephalic dysfunction
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Other Therapeutic Interventions with Insufficient Evidence
- Structures sensory Stimulation
- Hyperbaric Oxygen
- Repetitive TMS
- Dopaminergic/ Noradrenergic Agents
- GABAnergic Agents

Global Ischemia: Autonomic Instability
diencephalic or autonomic seizures, brainstem attack, central dysregulation, acute midbrain syndrome, tonic decerebrate spasms, tonic cerebellar fits, PSH, autonomic storming...

PSH: Paroxysmal Sympathetic Hyperactivity
- TBI (79.4%), hypoxia (9.7%), and stroke (5.4%)
- Hyperacute (24 hours) or Weeks after TBI
- Constellation of sx: fever, hypertension, tachycardia, dystonia, diaphoresis, arousal and behavioral changes indicative of autonomic dysfunction or sympathetic surges
- Can occur spontaneously or as a response to a stimulus
- Persistence is poor prognosticating factor for survival or functional outcomes
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PSH: Pathophysiology

- Influx of circulating catecholamine's post injury
- Higher order inhibitory pathways in cortex, diencephalon and upper brainstem are injured leading to unopposed sympathetic outflow from lower brainstem and spinal cord
- EIR (Excitatory/Inhibitory Ratio): Injured inhibitory pathways cause amplification/sensitization of sensory afferents from the spinal cord

TEMPERATURE REGULATION

- Anterior preoptic hypothalamus has heat sensitive neurons that promote sweating and ADH secretion
- Posterior hypothalamus has cold receptors that trigger shivering, vasoconstriction, and increase tone

PSH: Diagnostic Criteria

- Tachycardia >120 BPM (98%)
- Diaphoresis, fever, tachypnea, hypertension (71%)
- Dystonia and posturing (40%)
- Diagnosis hampered by poor clinician awareness and confusing nomenclature
- Diagnosis is still by exclusion (seizures, intracranial HTN, infection, HCP, pain, withdrawal)
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Clinical exam for source of infection
- CBC with differential
- Blood cultures
- Chest x-ray
- Abdominal films

CT scan of head
- Culture invasion lines, sputum, throat, urine
- Duplex scan, venogram of plethysmography for DVT
- Consider drug fever
- Extended chemistry profile and sedimentation rate
- Lumbar puncture (if indicated by clinical exam)
- Arterial blood gas and V/Q scan

Figure 1. Diagnostic fever protocol in TBI patients

Temperature > 38.2°C
- Clinical exam for source of infection
  - CBC with differential
  - Blood cultures
  - Chest x-ray
  - Abdominal films

CT scan of head
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Figure 1. Diagnostic fever protocol in TBI patients

Temperature > 38.2°C
- Clinical exam for source of infection
  - CBC with differential
  - Blood cultures
  - Chest x-ray
  - Abdominal films

Consider trial of bromocriptine, amantadine or dantrolene sodium
- Culture invasion lines, sputum, throat, urine
- Rapid resolution of autonomic signs and defervescence
- Extended chemistry profile and sedimentation rate
- Lumbar puncture (if indicated by clinical exam)
- Arterial blood gas and V/Q scan
- PTH

Rapid resolution of autonomic signs and defervescence
- Continue investigation
- Infectious Disease Consult

Yes
No

PSH Treatment: 3 Prong Approach

1. Inhibit afferent sensory processing to limit the development of allodynia
2. Inhibit central sympathetic outflow
3. Block end organ responses to the sympathetic nervous system

Infectious Disease Consult

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PSH : Treatment Approaches
Symptomatic
- Fever: Acetaminophen, NSAIDS, Dantrolene NA
- Tachycardia: Beta Blockers
- Hypertension: Beta Blockers, alpha blockers, hydralazine
- Spasticity: Baclofen
- Agitation/Restlessness: Beta Blockers, DA blockers

Centrally Acting
- Dopaminergic Agents: Bromocriptine / Amantadine
- GABAergic agents: Neurontin / Benzodiazepines
- AED's: Levetiracetam
- Opioid Agonists

PSH : Management and Outcomes
- Additional Comorbidities: Cardiac damage, Weight Loss, nutritional deficiencies, skin breakdown
- Early detection leads to decreased morbidity and long term disability
- PSH associated with longer Acute stay, higher prevalence of infections, longer ventilatory support, higher tracheostomy incidence
- In IPR, PSH did not impact recovery and functional status but were likely to require psychoactive meds

Global Ischemia: Movement Disorders
### Movement Disorders

- **Non Neurologic Causes:** Meds, Multi organ failure, cardioembolic events
- **Post Arrest Neurogenic Disorders:** PD, Dystonia, Chorea, Athetosis, tics, tremors, myoclonus
- **Most Studied and Documented:** Post Hypoxic Myoclonus (Acute and chronic)
- **Lance Adams (1963):** sustained myoclonus, dysmetria, ataxia and dysarthria

### Post Hypoxic Myoclonus

- **Myoclonus:** Sudden Shock like, involuntary movements
- **Focal, multifocal or generalized
- **Spontaneous vs Reactive
- **Resting, volitional or Postural
- **Positive vs Negative (EMG)

### Acute Posthypoxic Myoclonus

- **Begins within 24 hours of Cardiac Arrest (30-40%)**
- **Severe generalized violent flexion myoclonic movements including limbs, torso and face**
- **> 30 min = Myoclonic Status Epilepticus**
  - Poor prognosis for survival or emergence (90% mortality)
  - EEG findings +/- Epileptiform discharge, spikes and suppression patterns = neuronal death
  - Treatment: IV AEDs, Paralytic agents, Benzodiazepines
  - Damage to cortex, BG and thalamus, Hippocampus and Cerebellum
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Chronic Posthypoxic myoclonus: Lance Adams
- Occurs within a few days to a few weeks
- Action myoclonus involving the limbs, Stimulus sensitive myoclonus, Negative myoclonus
- Cortical myoclonus (distal extremity) vs Subcortical (proximal limbs and trunk)

PHM: Theories
- Serotonin
  - Low levels of 5-HIAA in CSF of PMH patients
  - 5-HTP treatment / 5HT modulation ameliorates PMH
  - Role of Estrogen in Serotonin modulation
- Phenylalanine
  - Reduced uptake is related to increased myoclonus
- Radiographic Correlates:
  - Increased glucose metabolism in ventrolateral thalamus in Purkinje Cell death

PMH Treatment Options
- Membrane Stabilizing Agents
  - Valproate, Levetiracetam
- GABAnergic Agents
  - Clonazepam/Zolpidem
- Serotonergic Agents
  - 5HTP
- Dopaminergic Agents (+/-)
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COMA vs VEGETATIVE vs MCS