Hypoxic Ischemic Encephalopathy

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Learning Objectives

- **Know the etiology of hypoxic-ischemic encephalopathy (HIE)**
- **Know the criteria used to diagnose and grading of HIE**
- **Be able to describe the pathophysiology of post hypoxic brain injury**
- **Know how hypothermia is used for neuroprotection and the criteria for using it**
- **Become familiar with the results of trials of other neuroprotective agents**

Definitions

- **Hypoxia or Anoxia:** A partial (hypoxia) or complete (anoxia) lack of oxygen in the brain or blood
- **Asphyxia:** The state in which placental or pulmonary gas exchange is compromised or ceases altogether
- **Ischemia:** The reduction or cessation of blood flow to an organ which compromises both oxygen and substrate delivery to the tissue
- **Hypoxic-Ischemic Encephalopathy:** Abnormal neurologic behavior in the neonatal period arising as a result of a hypoxic-ischemic event.

Pathogenesis

- Impaired cerebral blood flow (CBF) is the principal pathogenetic mechanism underlying most of the neuropathology attributed to perinatal brain injury. It is most likely to occur as a consequence of interruption of placental blood flow and gas exchange

Etiology of HIE

- Maternal:
  - Cardiac arrest
  - Asphyxiation
  - Severe anaphylaxis
  - Status epilepticus
  - Hypovolemic shock
- Uteroplacental:
  - Placental abruption
  - Cord prolapse
  - Uterine rupture
  - **Hyperstimulation with oxytocic agents**
- Fetal:
  - Fetomaternal hemorrhage
  - Twin to twin transfusion
  - Severe isoimmune hemolytic disease
  - Cardiac arrhythmia

Incidence of HIE

- **Occurs in 1-6 per 1000 live term births in developed countries**
  - **25% die or have multiple disabilities**
  - **4% have mild to moderate forms of cerebral palsy**
  - **10% have developmental delay**

Pathophysiology

- **The immature brain is in some ways more resistant to hypoxic-ischemic events compared to older children & adults**
  - **This may be due to:**
    - **Lower cerebral metabolic rate**
    - **Immaturity in the development of the balance of neurotransmitters**
    - **Plasticity of the immature CNS**

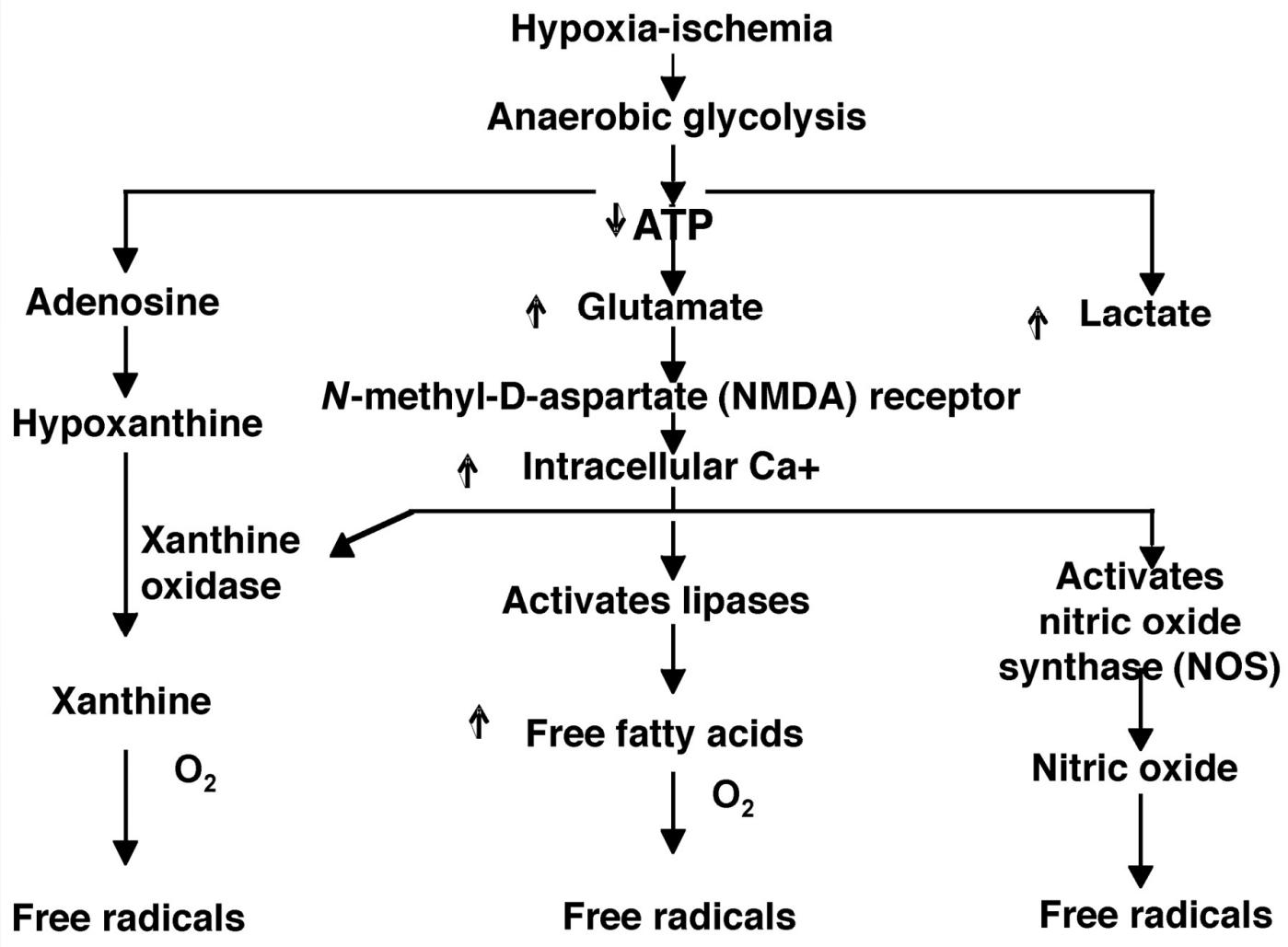
Pathophysiology

- **Gestational age plays an important role in the susceptibility of CNS structures**
  - **< 20 weeks: Insult leads to neuronal heterotopia or polymicrogyria**
  - **26-36 weeks: Insult affects white matter, leading to periventricular leukomalacia**
  - **Term: Insult affects primarily gray matter**

Pathophysiology

- **Other factors that influence the distribution of CNS injury:**
  - **Cellular susceptibility (neuron most susceptible)**
  - **Vascular territories (watershed areas)**
  - **Regional susceptibility (areas of higher metabolic rates, ie. Thalamus)**
  - **Degree of asphyxia**

Potential pathways for brain injury after hypoxia-ischemia.

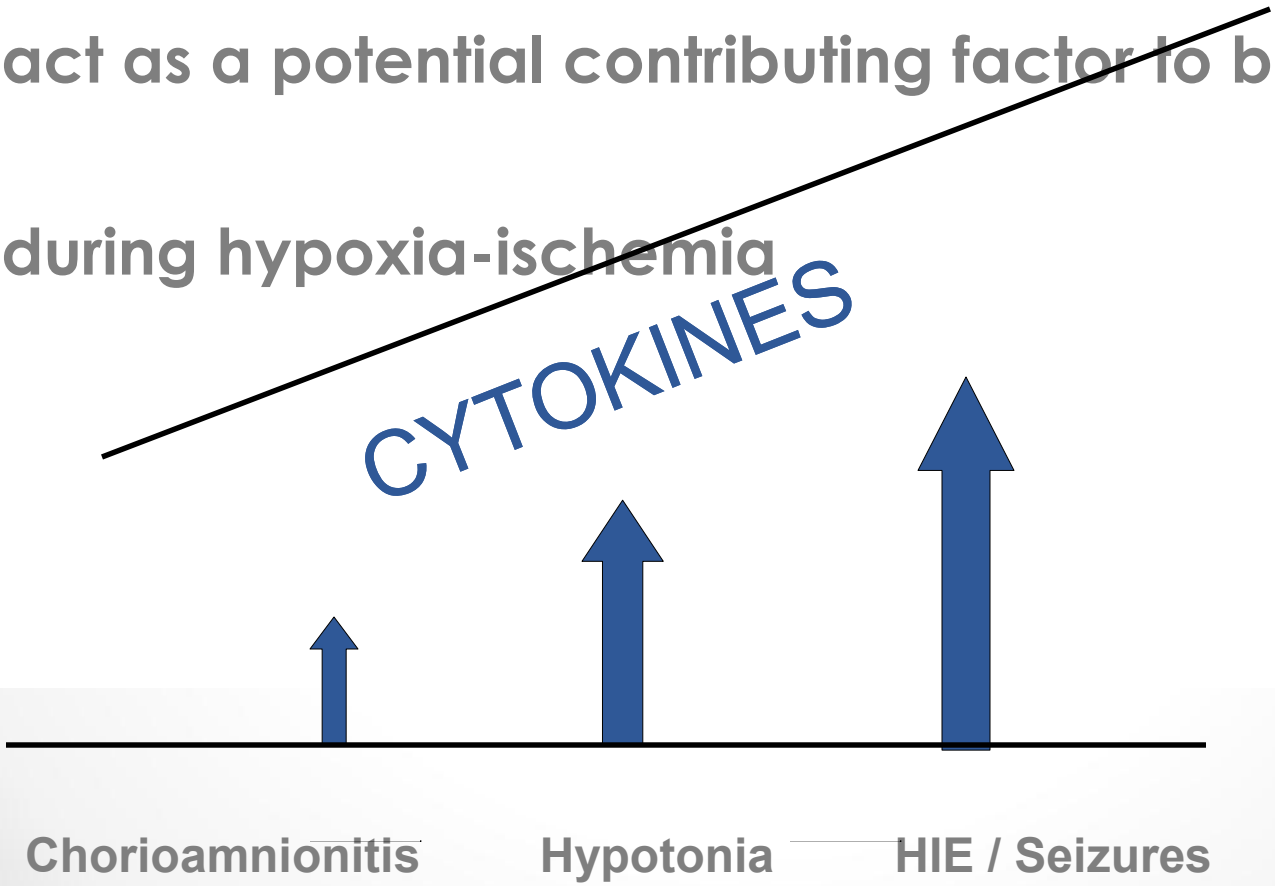


Perlman J M Pediatrics 2006;117:S28-S33

PEDIATRICS®

Pathophysiology

- Infection and/or the fetal inflammatory response act as a potential contributing factor to brain injury during hypoxia-ischemia



Diagnosis

- **The ability to identify infants at highest risk for progressing to hypoxic-ischemic encephalopathy is critical**
- **The therapeutic window i.e. that time whereby intervention strategies may be effective in preventing the processes of ongoing injury in the newborn brain is short and considered to be less than six hours**

Early Identification of High Risk Infants

- 1) Evidence of an Acute Perinatal Insult
-
- Indicated by a combination of markers
- 1) Sentinel event
- 2) Delivery room resuscitation by ambo
- 3) 5 Minute Apgar score ≤ 3
- 4) Cord arterial pH ≤ 7 or base deficit of >12)
-
- +
- 2) Postnatal evidence of encephalopathy
-
- 1) Clinical (Early onset of encephalopathy
- Multisystem organ dysfunction
- 2) EEG

Clinical Staging of HIE (Sarnat and Sarnat, 1976)

Table-1: Sarnat and Sarnat classification of HIE grading

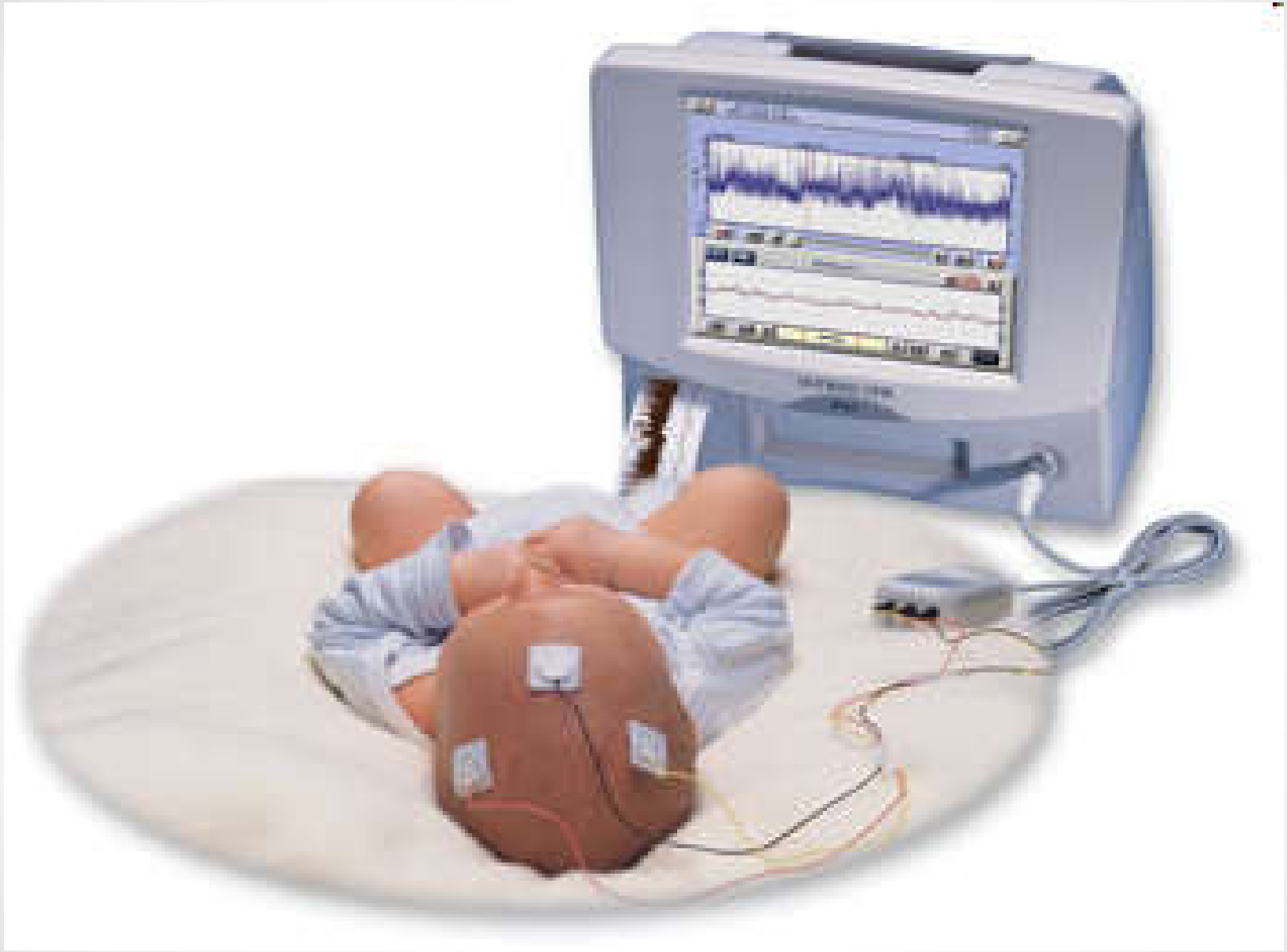
	STAGE- 1	STAGE-2	STAGE-3
Level of Consciousness	Hyper alert	Lethargic or obtunded	Stuporous
Neuromuscular Control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex Reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalised sympathetic	Generalised parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart Rate	Tachycardia	Bradycardia	Variable
GI Motility	Normal or decreased	Increased; diarrhoea	Variable
Seizures	None	Common; focal or multi-focal	Uncommon (excluding decerebration)
EEG Findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-Hz spike-and-wave	Early: periodic pattern with Isopotential phas Later: totally isopotential
Duration	1–3 days	2–14 days	Hours to weeks

Systemic Complications of HIE

- **CNS, convulsion, early hypotonia, late spasticity**
- **Acute renal failure in up to 20% of asphyxiated term infants**
- **Feeding intolerance occur in most of cases due to mesenteric blood vessels ischemia**
- **Elevated Liver Function tests in 80% of cases in full term**
- **Myocardial dysfunction and hypotension in 28-50% of term infants**
- **Coagulation impairment is relatively common in severely asphyxiated infants**
- ***Supportive care required!!***

Assessment Tools in HIE

- **Amplitude-integrated EEG (aEEG)**
  - **When performed early, it may reflect dysfunction rather than permanent injury**
  - **Most useful in infants who have moderate to severe encephalopathy**
    - **Marginally abnormal or normal aEEG is very reassuring of good outcome**
    - **Severely abnormal aEEG in infants with moderate HIE raises the probability of death or severe disability from 25% to 75%**



Assessment Tools in HIE

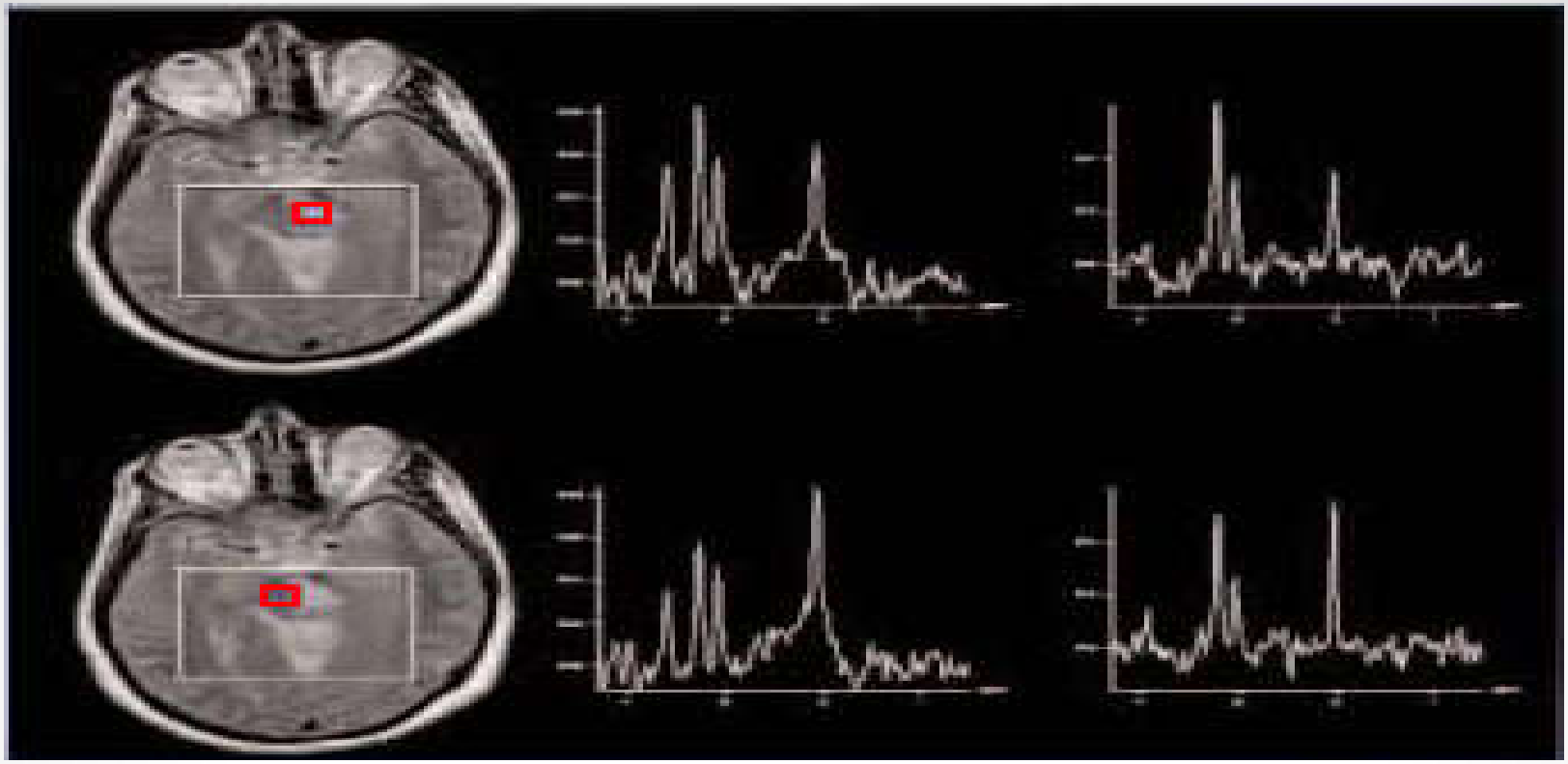
- **Neuroimaging**
  - **Cranial ultrasound: Not the best in assessing abnormalities in term infants. Echogenicity develops gradually over days**
  - **CT: Less sensitive than MRI for detecting changes in the central gray nuclei**

Assessment Tools in HIE

- **MRI: Most appropriate technique and is able to show different patterns of injury. Presence of signal abnormality in the internal capsule later in the first week has a very high predictive value for neurodevelopmental outcome**

Assessment Tools in HIE

- Magnetic Resonance Spectroscopy (MRS) provides a non-invasive method of studying metabolism in vivo.
- The tissue's chemical environment determines the frequency of a "metabolite peak" in an MRS "spectrum".



The lesion spectra demonstrate decreased NAA (a marker of neuronal integrity) and increased choline (a marker of myelin breakdown). The short TE spectrum demonstrates elevated myo-inositol (a marker of glial cells).

Management

- Initial resuscitation and stabilization, treatment of HIE is largely supportive and should focus on the following:
- Adequate ventilation
- Perfusion and blood pressure management - Studies indicate that a mean blood pressure (BP) above 35-40 mm Hg is necessary to avoid decreased cerebral perfusion
- Careful fluid management
- Avoidance of hypoglycemia and hyperglycemia
- Treatment of seizures (**see later)**
- Hypothermia management

Management - Hypothermia

- **Has become standard of care**
- **Whole-body and head-cooling** available
  - Unclear if one regimen is superior to the other - currently either one is utilized, based on availability
- **Aim to get core (rectal) temperature to 33-35° C for 72 hours for moderate hypothermia**
  - ***based on Cool Cap and NICHD Neonatal Research Network trials***

Hypothermia - Mechanism of Action

- **Reduces cerebral metabolism, prevents edema**
- **Decreases energy utilization**
- **Reduces/suppresses cytotoxic amino acid accumulation and nitric oxide**
- **Inhibits platelet-activating factor, inflammatory cascade**
- **Suppresses free radical activity**
- **Attenuates secondary neuronal damage**
- **Inhibits cell death**
- **Reduces extent of brain damage**
  - **DEATH OR SEVERE DISABILITY AT 18 MONTHS OF AGE SIGNIFICANTLY REDUCED!!**

Criteria for Hypothermia

- **Infant must be 35 weeks gestation or more**
- **Infant must have 2 of the following:**
  - **Apgar score of 5 or less at 5 minutes**
  - **Mechanical ventilation or resuscitation at 10 minutes**
  - **Cord or arterial pH <7.15 or base deficit of 12 or more within 60 minutes of birth**
- **Cooling must be started within 6 hours of birth**
- **Core temp goal of 33-35°C for 72 hours**

Questions

1. **The mother of a baby with suspected HIE inquires about the possibility of a brain insult in her infant. Of the following, the single most useful predictor of brain insult in this infant is the evidence of:**

    A. Abnormal neurologic exam findings

    B. Cerebral edema on cranial US

    C. Elevated creatinine phosphokinase

    D. Hemodynamic and pulmonary imbalance

    E. Multisystem organ dysfunction

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Questions

2. **The severity of HIE can be graded as mild, moderate, or severe, using a classification proposed by Sarnat and Sarnat. Of the following, the criterion *most* consistent with the diagnosis of mild HIE is:**

   A. Absence of seizures

   B. Low Apgar scores

   C. Need for assisted ventilation

   D. Proximal muscle weakness

   E. Obtunded state of consciousness

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Questions

3. **Several ancillary tests have been proposed to improve the prediction of long-term outcome of infants who have suffered from HIE. Of the following, the *most* useful and practical test for determining the prognosis of HIE is:**

   A. Cranial ultrasound

   B. MRI

   C. EEG

   D. Near-infrared spectroscopy

   E. Somatosensory evoked potentials

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References

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Thank you

Neonatal convulsion

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Definition

- A stereotypic, paroxysmal spell of altered neurologic function (behavior, motor,and/or autonomic function)

Basic Mechanisms of Seizures

- Abnormal energy production (hypoxemia, hypoglycemia)
- Alteration in neuronal membrane (hypocalcemia, hypomagnesemia)
- Relative excess of excitatory versus inhibitory neurotransmitters (GABA)

Incidence

- Higher in neonates than any other age group
- Most frequent in the first 10 days of life

Do Prolonged Seizures Harm the Developing Brain?

- Animal studies:
  - Persistent neonatal seizures in rats induce neuronal death and changes in hippocampus
- Chronic seizures in adults associated with memory impairment and poor psychosocial outcome
- Permanent reduction in seizure threshold associated with significant deficits in learning and memory

Causes of Neonatal Seizures

1. HIE (32%)
2. Intracranial hemorrhage (17%)
3. CNS infection (meningitis, TORCH) (14%)
4. Infarction (7%)
5. Metabolic disorders (6%) as (as hypoglycemia & hypocalcaemia, Vitamin B6 seizures)
6. Inborn errors (3%) (mentions)
7. Unknown (10%) Benign idiopathic convulsion, benign familial seizures
8. Drug withdrawal (1%)

Classification

I. Clinical Seizure

- Subtle
- Tonic
- Clonic
- Tonic-clonic
- Myoclonic

Subtle Seizures

- More in preterm than in term
- Eye deviation (term)
- Blinking, fixed stare (preterm)
- Repetitive mouth and tongue movements
- Apnea
- Bicycling movements and tonic posturing of limbs

Benign Sleep Myoclonus

- Condition mimic convulsion
- Onset 1st week of life
- Synchronous jerks of upper and lower extremities during sleep
- No EEG correlate
- Provoked by benzodiazepines
- Ceases upon arousal
- Resolves by 2 months
- Good prognosis

Jitteriness vs. Seizures

- No ocular phenomena
- Not occur in the face
- Stimulus sensitive
- Tremor movement
- Movements cease with passive flexion

Jitteriness Versus Seizure

CLINICAL FEATURE	JITTERINESS	SEIZURE
Abnormality of gaze or eye movement	O	+
Movements exquisitely stimulus sensitive	+	O
Predominant movement	Tremor	Clonic jerking
Movements cease with passive flexion	+	O
Autonomic changes	O	+

Epileptic syndromes-benign

- **Benign familial neonatal seizures**
  - Autosomal dominant
  - Inter and post-ictal exam is normal
  - Long term outcome is good
  - Unusual tonic-clonic pattern
- **Benign idiopathic neonatal seizures**
  - Term, normal birth
  - Normal inter and post-ictal state, EEG
  - Clonic, occur day 5, good prognosis
  - So called 5th day convulsion

Epileptic syndromes-malignant

- **Neonatal Myoclonic encephalopathy**
  - Fragmentary partial seizures, massive myoclonus
  - Metabolic disorders, abnormal EEG
  - Poor prognosis
- **Ohtahara syndrome**
  - 10d -3 mo
  - Numerous brief Tonic seizures
  - Dysgenesis is cause, prognosis very poor

Investigations

- Blood glucose, calcium, magnesium, sodium, urea & creatinine.
- Arterial blood gases
- Blood culture
- Lumber puncture (if not contraindicated)
- Cranial ultrasound
- Brain computerized tomography (CT)
- Brain magnetic resonance imaging (MRI)
- Electro-Encephalography (EEG)

Treatment

- Resuscitation and general supportive care if needed.(mention)
- Treatment of the cause (mention as hypoglycemia, hypocalcaemia, meningitis)
- Anticonvulsants therapy:
  - Drugs must be given IV
    - Phenobarbitone:
      - Loading dose: 20 mg/kg IV
      - Maintenance dose: 5 mg/kg IV or oral
    - Phenytoin:

      Loading dose: 20mg/kg IV very slowly diluted with saline
      - Maintenance dose: 5 mg/kg IV divided into 2 doses

Treatment

- **Lorazepam (Ativan)**

  bolus 0.05mg/kg and may be repeated

- **Mediazolm (Dormicum)**

  Loading dose 0.1mg/kg and may be repeated

  continuous infusion by rate 1-2 mcg/kg/min

- **Pyridoxine therapy (Vitamin B6)**

  When the seizures prove to refectory to the proceeding regimen pyridoxine IV 50-100mg given

Prognosis based on etiology

- Hypoxia-ischemia
- Meningitis
- Hypoglycemia
- Early Hypocalcemia

50% normal outcome

- Subarachnoid hemorrhage
- Late Hypocalcemia

Almost all are normal

Thank You